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(54) Title: USE OF 17-KETOSTEROID COMPOUNDS AND DERIVATIVES, METABOLITES AND PRECURSORS THEREOF IN THE TREATMENT OF HEPATITIS C VIRUS AND OTHER TOGAVIRUSES

(57) Abstract

The invention provides the use of 17-ketosteroid compounds, as well as derivatives, metabolites and precursors of such compounds, and pharmaceutically acceptable salts of any of these compounds, collectively defined herein as the "compounds of the present invention", in the treatment of prevention of hepatitis C type virus and/or hepatitis G type virus in patients in need of such treatment. In addition, the invention provides methods to treat or prevent togavirus infections, including infections by one or more alphaviruses, flaviviruses, such as yellow fever virus, hepatitis C virus and hepatitis G virus, rubella viruses, or pestiviruses, such as bovine virus diarrhea virus. In addition, the invention provides combination therapies including administration of one or more compound of the present invention, as defined herein, and administration of one or more compound selected from plasma concentration-enhancing compounds, macrophage stimulating factor, oxidation agents, ribavirin and alpha interferon, and/or oxygen ventilation. The compounds of the present invention may also be used to ameliorate or reduce one or more symptoms associated with a togavirus infection.

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USE OF 17-KETOSTEROID COMPOUNDS AND DERIVATIVES, METABOLITES AND PRECURSORS THEREOF IN THE TREATMENT OF HEPATITIS C VIRUS AND OTHER TOGAVIRUSES

BACKGROUND OF THE INVENTION

The present invention relates to steroid compositions and methods to use them to treat flavivirus and togavirus infections, such as human hepatitis C virus ("HCV") infections.

The present invention is directed to the use of 17-ketosteroid compounds, as well as derivatives, metabolites and precursors of such compounds, and pharmaceutically acceptable salts of any of these compounds, collectively defined herein as the "compounds of the present invention", optionally together with one or more additional chemical agents and/or treatment methods (as described below) in the treatment of hepatitis C type virus and/or hepatitis G type virus in patients in need of such treatment. In addition, the present invention is directed to methods of treatment of togaviruses, including alphaviruses (also known as arboviruses, group A), flaviviruses (also known as arboviruses, group 13)(such as yellow fever, as well as hepatitis C and hepatitis G), rubiviruses (also known as rubella viruses)(such as rubella) and pestiviruses (also known as mucosal disease viruses)(such as bovine virus diarrhea virus (BVDV)).

There is an ongoing need for methods of treatment of hepatitis C virus, which are safer and/or more effective than known methods of treatment. As stated by C. Everett Koop, former U.S. Surgeon General, "we stand at the precipice of a grave threat to our public health... It affects people from all walks of life, in every state, in every country. And unless we do something about it soon, it will kill more people than AIDS", Koop, Hepatitis C, - An Epidemic for Anyone. As stated in Maddrey, W.C. et al, "Beyond Monotherapy: Next Generation Therapies for Chronic Hepatitis C", unfortunately, the only therapy offered in the U.S. National Institutes of Health Consensus Development Statement on the Management of Hepatitis C, published in March, 1997, has proven ineffective for the majority of patients-not only have a significant proportion of patients failed to respond to this treatment, but another sizable segment has relapsed or had limited response. Because not all patients with chronic hepatitis C virus infection respond to standard treatment with interferon alfa ("IFNα"), new therapeutic strategies are needed Di Bisceglie, A.M., "Emerging Therapies for Chronic Hepatitis C".

Hepatitis C virus infection is extremely common, with estimates of worldwide prevalence of chronic hepatitis ranging from 90 million up to over 200 million (2 % to 4 %). There is no vaccine or candidate vaccine for pre-exposure prophylaxis and no effective globulin for post-exposure prophylaxis.

The major liability of HCV infection is the propensity to develop chronic hepatitis in at least 75 % of the cases; virtually all infected patients may be chronically infected. It is theorized that HCV-related liver injury is directly or indirectly related to cytotoxic Tlymphocytes (CTL)

directed at viral peptides expressed on the hepatocyte membrane. These CTL are localized within the liver, are present in small numbers, and are probably only transiently effective since the virus is so heterogeneous and mutates at such a rapid rate. In view of this, purely antiviral compounds, such as nucleoside analogues or enzyme inhibitors, are likely to be virostatic but unlikely to eliminate infection. In addition, immune directed therapies such as antibody preparations or cellular immune stimulants are likely to be transiently effective due to changes or mutations in the virus.

Chronic hepatitis C is insidiously progressive. In general, infection progresses to chronic hepatitis, cirrhosis, liver failure, and hepatocellular carcinoma over a period of decades, not months or years.

A reliable and effective cell culture for HCV does not exist. In addition, no nonprimate animal model exists. As a result, few agents have been tested against HCV. It is known that acyclovir, ribavirin, and corticosteroids are ineffective, and that corticosteroids increase the level of HCV replication.

Interferons have been used in the treatment of chronic hepatitis C. Interferons are natural glycoproteins produced by cells in response to infection by viruses. Interferons inhibit the replication of a wide spectrum of RNA and DNA viruses, including hepatitis viruses. This occurs via a variety of mechanisms including inhibition of virus attachment and uncoating, induction of intracellular proteins and ribonucleases which convey antiviral properties to the cell, and amplification of both specific (cytotoxic T-lymphocyte) and nonspecific (natural killer cell) immune response to viral proteins. The specific mechanism of interferon activity in chronic hepatitis C infection is not known.

Because of its known antiviral properties and the experience with interferon in the treatment of other forms of viral hepatitis, interferon was evaluated as a potential treatment for patients with non-A, non-B hepatitis before the hepatitis C virus was even identified. Several reports indicate that a response during interferon therapy can be expected in about 40 % of chronic hepatitis C patients, and this response generally occurs quickly. HCV RNA levels fall dramatically and become undetectable within 4 - 8 weeks in the majority of patients who subsequently normalize their serum aminotransferases.

Despite the prompt antiviral and biochemical response to treatment and the inability to detect residual HCV in either liver or serum in responding patients, biochemical normalization and absence of detectable viremia in serum is maintained in only a minority of patients ranging from 8 - 35 %. Relapse characterized by a rebound in serum ALT out of the normal range occurs in 50 - 90 % of "successfully" treated patients following the discontinuation of interferon treatment.

At least half of patients with chronic hepatitis C who are treated with interferon fail to respond. Some patients who initially appear to respond to interferon by normalizing serum ALT levels will demonstrate a progressive rise in the serum ALT levels despite continuation of interferon.

A variety of factors have been examined for their relation to whether a patient responded to interferon, including age, gender, body mass, pre-treatment HCV-RNA level, extent of loss of HCV-RNA during the start of treatment, viral genotype, absence or presence of fibrosis or cirrhosis, dosage of interferon, serum ferritin levels and hepatic iron levels, but none of these has been able to predict accurately and consistently which HCV patients will respond to interferon.

Furthermore, there are many cases where administering interferon alone for treatment of hepatitis C appears to be detrimental to patients, and sometimes very harmful to patients. For example, use of interferon in patients with predominant autoimmune features can intensify an immune-mediated hepatocullular inflammation (see Shindo et al, "Acute exacerbation of liver disease during interferon alfa therapy for chronic hepatitis C" Gastroenterology 1992; 102: 1406-1408). Interferon can transform chronic viral hepatitis into an autoimmune hepatitis (Silva et al, "Interferon-induced chronic active hepatitis?" Gastroenterology 1991; 101: 840-8-42). Administering interferon can also induce production of a variety of autoantibodies of uncertain clinical significance (Mayet et al, "Treatment of chronic type B hepatitis with recombinant alpha-interferon induces autoantibodies, not specific for autoimmune chronic hepatitis," Hepatology 1989;10:24-28), all of which are incorporated herein by reference. Interferon causes an increase in HLA display on membrane surfaces, impairs suppressor T cell function, enhances autoantibody production, stimulates natural killer cell function, affects cytokine release, and activates macrophages, making it capable of worsening an immune-mediated disease (Baron et al., "The interferons: mechanisms of action and clinical applications," JAMA 1991; 266:1375-1383, which is incorporated herein by reference). In still other patients, such as those with normal serum ALT levels or decompensated disease, the advantages of therapy are unproved and doubtful.

In addition, from studies of its use in other therapies, interferon has a number of well-known side effects, including fever, chills, flu like syndrome, fatigue, anorexia, worsening in performance status, nausea and vomiting, weight loss, leukopenia, anemia, neurological symptoms, psychological symptoms and dyspnea. See, e.g., Tsavaris, N. et al, "Treatment of renal cell carcinoma with escalating doses of alpha-interferon," Chemotherapy, 1993 Sep-Oct; 39 (5): 361-6. In addition, interferon has been linked with the development of thyroid disease in HCV patients. Lisker-Melman M, et al., "Development of thyroid disease during therapy of chronic viral hepatitis with interferon alfa". Gastroenterology 1992 Jun;102(6):2155-60.

Ribavarin is a compound which is reported to have a broad spectrum of in vitro activity against both RNA and DNA viruses, including flaviviridae related to hepatitis C. Pilot studies reported reduction of both serum ALT and HCV RNA levels in patients with chronic HCV infection, but in a subsequent randomized controlled trial, the antiviral effect of ribavirin alone could not be confirmed. Several subsequent small studies appear to demonstrate a synergistic effect of ribavirin and interferon in patients with hepatitis C infection, however, the risks and side effects of interferon monotherapy remain as important drawbacks.

Several agents or maneuvers including ursodeoxycholic acid, indomethacin, nacetyl-cysteine, silymarin, several herbal preparations and phlebotomy have been reported to be useful adjuncts to interferon treatment, but none of these have been consistently shown to be effective in controlled trials.

Hepatitis G virus (HGV; also called hepatitis GB virus C or HGBV-C) was fully characterized in early 1996. HGV is a flavivirus and a distant relative of HCV. At this time, HGV infection can be identified only through PCR testing, which indicates current infection. Such testing is not readily available or standardized. An antibody test for HGV is under development and, when available, will elucidate the epidemiology of HGV infection more fully than HGV RNA testing can. It appears that once antibodies are found, HGV RNA is usually no longer present.

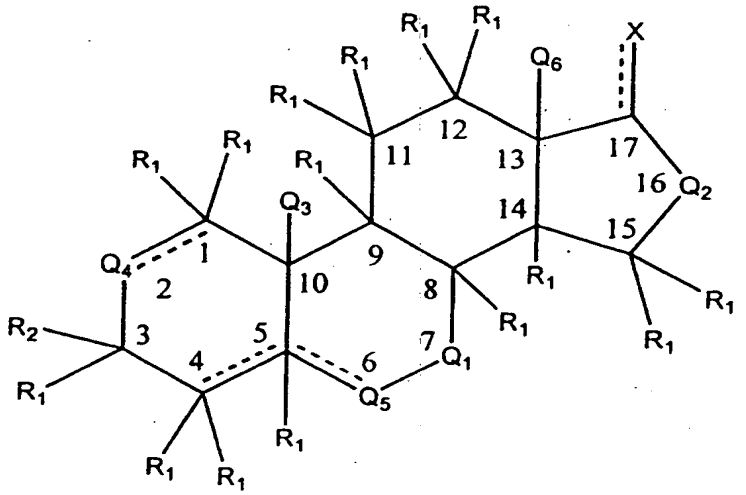
Transmission of HGV through blood transfusion has been documented (the only Canadian study indicated that infection may occur in 1 in 1500 transfusion recipients and account for 9% of post-transfusion hepatitis), and from mother to child in the perinatal period. There is an increased prevalence of HGV RNA among groups with frequent exposure to blood or blood products (e.g., persons with hemophilia or thalassemia, patients on hemodialysis and injection drug users). Other modes of transmission (e.g., sexual) are possible but have not been well documented. Coinfection with HBV, HCV, or both is common and likely represents similar modes of transmission. In 0.3% of cases of community-acquired acute viral hepatitis, HGV is the only identified agent.

A number of steroid compounds and their uses have been described. See, e.g., U.S. patent numbers 4956355, 5859000, 4268441, 4666898, 5837269, 5827841, 5811418, 5824313, 5686438, 5635496, 5587369, 5583126, 5562910, 5532230, 5518725, 5736537, 5843932, 5837700, 5824671, 5807849, 5798347, 5780460, 5776923, 5728688, 5610150, 5593981, 5372996, 5110810, 5807848, 5707983, 5641766, 5585371, 5506223, 5424463, 5296481, 5292730, 5776921, 5641768, 5559107, 5478566, 5461042, 5407684, 5387583, 5277907, 5206008, 5077284, 5162198, 5660835, 5527789, 5756482, 5709878, 5804576, 5744462, 5714481, 5700793, 5696106, 5656621, 5175154, 5157031, 5028631, 5001119, 4898694, 5824668, 5710143, 5795880, 5527788, 5591736, 5861390 and PCT publication numbers WO 98/05338, WO 95/21617, WO 98/50040, WO 98/50041 and WO 97/48367, all of which are incorporated herein by reference.

A number of flavonoids, methods to obtain them and their uses have been described. See, e.g., J.A. Manthey and B.S. Buslig, editors, *Flavonoids in the living system, Advances in experimental medicine and biology*, volume 439, Plenum Press, New York, 1998, chapter 15 (pages 191-225), chapter 16 (pages 227-235) and chapter 17 (pages 237-247), which are incorporated herein by reference.

SUMMARY OF THE INVENTION

A principal embodiment of the invention provides a method to treat or prevent a togavirus infection comprising administering to a subject an effective amount of a compound(s) of formula 1,



1

wherein

Q_1 is $-C(R_1)_2-$ or $-C(O)-$;

Q_2 is $-C(R_1)_2-$, $-C(R_1)(Y)-$, $-C(Y)-$ or $-CH_2-CH_2-$;

Q_3 is $-H$ or $-C(R_1)_3-$;

Q_4 is $-C(R_1)_2-$, $-C(O)-$, hydroxyvinylidine ($-CH(CH=CHOH)-$) or methyl methylene ($-CH(CH)_3-$);

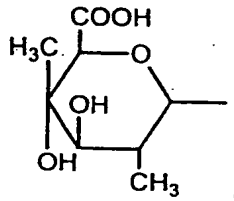
Q_5 is $-C(R_1)_2-$ or $-C(O)-$;

X and Y independently are -OH, -H, lower alkyl (e.g., C_{1-6} alkyl), $-O-C(O)-R_5$, $-C(O)-OR_5$, halogen (i.e., -F, -Cl, -Br or -I) or =O;

each R_1 independently is -H, -F, -Cl, -Br, -I, -OH, C_{1-6} alkoxy, or C_{1-6} alkyl;

R_2 is -H, -OH, -F, -Cl, -Br, -I, C_{1-6} alkyl, C_{1-6} alkoxy, $-OR_3$, an ester (e.g., $-O-C(O)-R_4$ or $-C(O)-O-R_4$), a thioester (e.g., $-O-C(S)-R_4$ or $-C(S)-O-R_4$), a thioacetal (e.g., $-S-C(O)-R_4$ or $-C(O)-S-R_4$), a sulfate ester (e.g., $-O-S(O)(O)-O-R_4$), a sulfonate ester (e.g., $-O-S(O)-O-R_4$) or a carbamate (e.g., $-O-C(O)-NH-R_4$ or $-NH-C(O)-O-R_4$) or R_2, together with the R_1 that is bonded to the same carbon atom is =O;

R_3 is $-S(O)(O)-OM$, $-S(O)(O)-O-CH_2-CH(O-C(O)-R_6)-CH_2-O-C(O)-R_6$, $-P(O)(O)-O-CH_2-CH(O-C(O)-R_7)-CH_2-O-C(O)-R_7$, a glucuronide group of structure (A)



(A),

or R_3 is C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, a C_{1-18} ester or a C_{1-18} thioester, where any of the foregoing C_{1-18} or C_{2-18} moieties are optionally substituted at one or more hydrogen atoms with one or more independently selected $-OR^{PR}$, (including -OH), $-NHR^{PR}$, (including $-NH_2$) or $-SR^{PR}$,

(including -SH) groups, or R_3 is a C_{1-18} fatty acid, C_{2-10} alkynyl, $(J)_n$-phenyl-C_{1-5}-alkyl, $(J)_n$-phenyl-C_{2-5}-alkenyl;

R_4 is -H, a protecting group, optionally substituted C_{1-18} alkyl, optionally substituted C_{1-18} alkenyl, optionally substituted C_{1-18} alkynyl, optionally substituted aryl, optionally substituted aryl-C_{1-6} alkyl, optionally substituted aryl-C_{2-6} alkenyl, optionally substituted aryl-C_{2-6} alkynyl, optionally substituted heterocycle-C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl-heterocycle, optionally substituted C_{2-6} alkynyl-heterocycle or an optionally substituted heterocycle, where any of the foregoing moieties are optionally substituted at one, two, three, four, five or more carbon or hydrogen atoms with one or more independently selected -O-, -S-, $-NR^{PR}$- (including -NH-), -NH-C(O)-, $-OR^{PR}$ (including -OH), $-NHR^{PR}$ (including $-NH_2$), $-SR^{PR}$ (including -SH), =O, =S, =N-OH, -CN, $-NO_2$, -F, -Cl, -Br or -I groups or atoms;

each R_5 independently is straight or branched C_{1-14} alkyl;

each R_6 independently is straight or branched C_{1-14} alkyl;

each R_7 independently is straight or branched C_{1-14} alkyl or a glucuronide group of structure (A);

each R^{PR} independently is -H or an independently selected protecting group;

n is 0, 1, 2 or 3;

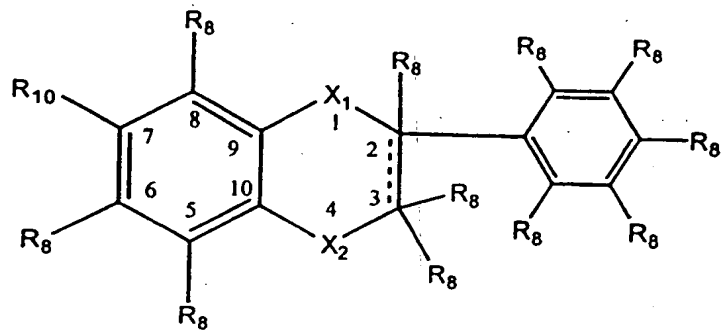
each J independently is -F, -Cl, -Br, -I, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, carboxy, nitro, sulfate, sulfonyl, a C_{1-6} carboxyl ester or a C_{1-6} sulfate ester;

M is hydrogen, sodium, $-S(O)(O)-O-CH_2-CH(O-C(O)-R_6)-CH_2-O-C(O)-R_6$, $-P(O)(O)-O-CH_2-CH(O-C(O)-R_7)-CH_2-O-C(O)-R_7$ or a glucuronide group of structure (A);

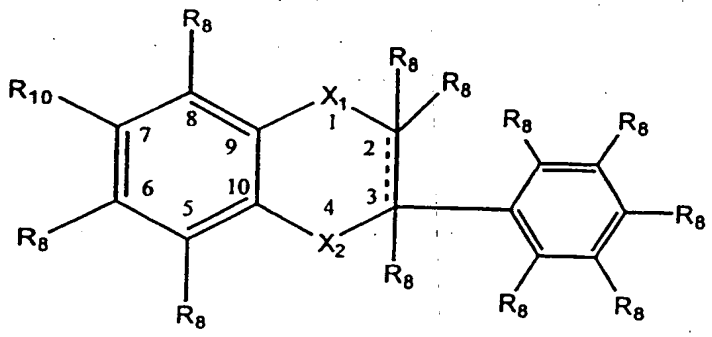
the dotted lines in formula 1 represent an optional double bond, provided that there are not double bonds at both the 4-5 and 5-6 positions and provided that when a double bond is present, zero or 1 R_1 group is bonded to carbon atoms at the 1-, 2-, 4-, 5-, 6- or 17 positions so that these carbon atoms are tetravalent; and

the salts, stereoisomers, positional isomers, metabolites, analogs, precursors, hydrates, tautomers, ionized forms and solvates thereof. The formula 1 compounds are collectively referred to herein as the "compounds of the invention" or "compounds of the present invention".

Another invention embodiment comprises a method to treat or prevent a togavirus infection comprising administering to a subject a compound of the invention simultaneously or sequentially with a compound of formula 2A or 2B



2A



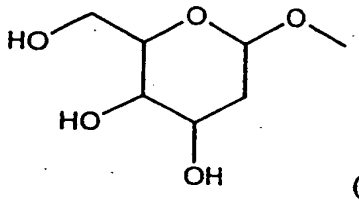
2B

wherein a double or a single bond is present at the dotted line and, when a double bond is present, (i) the optionally substituted phenyl ring at the 2- or 3-position is present and the R_8 that is bonded to the carbon is absent, and (ii) one R_8 at the adjacent 2- or 3-position is absent;

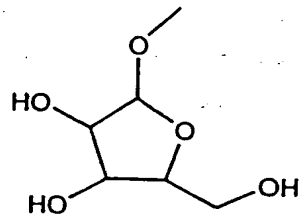
X_1 is -O- or $-C(R_8)_2-$;

X_2 is -C(O)- or $-C(R_{11})_2-$;

each R_8 independently is -H, -OH, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, glucuronide, a C_{1-25} fatty acid, the residue of a formula 2A or 2B compound where a hydrogen atom is removed to form the formula 2A or 2B compound radical, $-CH_2CH=C(CH_3)_2$, glucoside, a group having structure (B) or (C),



(B) or



(C)

R_{10} is C_{1-6} alkyl, C_{1-6} alkoxy, neohesperidoside, apioglucoside, rutinoside, glucoside, galactoside, rhamnoside, arabinoside, or a stereoisomer, hydrate, analog, derivative or metabolite of any of these moieties, any of which are optionally independently substituted at one or more hydrogen atoms with -OH, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, glucuronide or a C_{1-25} fatty acid or R_{10} is -H, -OH or halogen;

each R_{11} independently is -H, -OH, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, glucuronide, a C_{1-25} fatty acid, or both R_{11} together are =O; and

the salts, stereoisomers, positional isomers, metabolites, analogs, precursors, hydrates, tautomers, ionized forms and solvates thereof.

Another embodiment of the invention is a method to treat or prevent a togavirus infection, including one or more infections with alphaviruses, flaviviruses, rubiviruses or pestiviruses, comprising administering to a subject a compound of the invention (a formula 1 compound) and a macrophage stimulating factor and optionally also administering a formula 2A or 2B compound.

A further invention embodiment is a method to treat or prevent a togavirus infection, including one or more infections with alphaviruses, flaviviruses, rubiviruses or pestiviruses, comprising administering to a subject a compound of formula 1 and (1) administering an oxidation agent or (2) using oxygen ventilation and optionally also administering a macrophage stimulating factor(s) and/or a formula 2A or 2B compound.

Another invention embodiment is a method to treat or prevent a togavirus infection, including one or more infections with alphaviruses, flaviviruses, rubiviruses or pestiviruses, comprising administering to a subject a compound of formula 1 and ribavirin and/or αIFN and optionally also using one or more of a formula 2A or 2B compound, a macrophage stimulating factor, an oxidation agent or oxygen ventilation.

DETAILED DESCRIPTION OF THE INVENTION

As used herein and unless otherwise stated or implied by context, the following terms have the meanings defined here.

A "patient" or "subject" means a human or animal. Usually the animal is a vertebrate such as a primate, rodent, domestic animal or game animal. Primates include chimpanzees, cynomologous monkeys, spider monkeys, and macaques, e.g., *Rhesus*. Rodents include mice, rats, woodchucks, ferrets, rabbits and hamsters. Domestic and game animals include cows, horses, pigs, deer, bison, buffalo, felines, e.g., domestic cat, canines, e.g., dog, avians, e.g., chicken, emu, ostrich, and fish, e.g., trout, catfish and salmon. Patient or subject includes any subset of the foregoing, e.g., all of the above, but excluding one or more groups or species such as humans, primates or rodents.

"Alkyl" as used herein, unless stated to the contrary, is a C_1-C_{18} hydrocarbon containing 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 or 18 carbon atoms in the form of normal, secondary, tertiary, cyclic or mixed structures. Examples are $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-C(CH_3)_3$, $-CH_2CH_2CH_2CH_2CH_3$, $-CH(CH_3)CH_2CH_2CH_3$, $-CH(CH_2CH_3)_2$, $-C(CH_3)_2CH_2CH_3$, $-CH(CH_3)CH(CH_3)_2$, $-CH_2CH_2CH(CH_3)_2$, $-CH_2CH(CH_3)CH_2CH_3$, $-CH_2C(CH_3)_3$, $-CH_2CH_2CH_2CH_2CH_2CH_3$, $-CH(CH_3)CH_2CH_2CH_2CH_3$, $-CH(CH_2CH_3)(CH_2CH_2CH_3)$, $-C(CH_3)_2CH_2CH_2CH_3$, $-CH(CH_3)CH(CH_3)CH_2CH_3$, $-CH(CH_3)CH_2CH(CH_3)_2$, $-C(CH_3)(CH_2CH_3)_2$, $-CH(CH_2CH_3)CH(CH_3)_2$, $-C(CH_3)_2CH(CH_3)_2$, $-CH(CH_3)C(CH_3)_3$,

cyclopropyl, cyclobutyl, cyclopropylmethyl, cyclopentyl, cyclobutylmethyl, 1-cyclopropyl-1-ethyl, 2-cyclopropyl-1-ethyl, cyclohexyl, cyclopentylmethyl, 1-cyclobutyl-1-ethyl, 2-cyclobutyl-1-ethyl, 1-cyclopropyl-1-propyl, 2-cyclopropyl-1-propyl, 3-cyclopropyl-1-propyl, 2-cyclopropyl-2-propyl, and 1-cyclopropyl-2-propyl.

"Alkenyl" as used herein, unless stated to the contrary, is C_2-C_{18} hydrocarbon comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 or 18 carbon atoms in the form of normal, secondary, tertiary, cyclic or mixed structures and comprising 1, 2, 3 or more double bonds between adjacent carbon atoms. Examples are $-CH=CH_2$, $-CH=CHCH_3$, $-CH_2CH=CH_2$, $-C(=CH_2)(CH_3)$, $-CH=CHCH_2CH_3$, $-CH_2CH=CHCH_3$, $-CH_2CH_2CH=CH_2$, $-CH=C(CH_3)_2$, $-CH_2C(=CH_2)(CH_3)$, $-C(=CH_2)CH_2CH_3$, $-C(CH_3)=CHCH_3$, $-CH(CH_3)CH=CH_2$, $-C=CHCH_2CH_2CH_3$, $-CHCH=CHCH_2CH_3$, $-CHCH_2CH=CHCH_3$, $-CHCH_2CH_2CH=CH_2$, $-C(=CH_2)CH_2CH_2CH_3$, $-C(CH_3)=CH_2CH_2CH_3$, $-CH(CH_3)CH=CHCH_3$, $-CH(CH_3)CH_2CH=CH_2$, $-CH_2CH=C(CH_3)_2$, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, and 1-cyclohex-3-enyl.

"Alkynyl" as used herein, unless stated to the contrary, is C_2-C_{18} hydrocarbon comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 or 18 carbon atoms in the form of normal, secondary, tertiary, cyclic or mixed structures and comprising 1, 2, 3 or more triple bonds between adjacent carbon atoms. Examples are $-CCH$, $-CCCH_3$, $-CH_2CCH$, $-CCCH_2CH_3$, $-CH_2CCCH_3$, $-CH_2CH_2CCH$, $-CH(CH_3)CCH$, $-CCCH_2CH_2CH_3$, $-CH_2CCCH_2CH_3$, $-CH_2CH_2CCCH_3$ and $-CH_2CH_2CH_2CCH$.

"Halogen" or "halo" means fluorine (-F), chlorine (-Cl), bromine (-Br) or iodine (-I) and if more than one halogen is referred to (e.g., two or more variable groups may be a halogen), each halogen is independently selected.

"Steroid nucleus" means 4 fused rings having the formula 1 structure.

"PEG" means an ethylene glycol polymer that contains about 20 to about 2000000 linked monomers, typically about 50-1000 linked monomers, usually about 100-300. Polyethylene glycols include PEGs containing various numbers of linked monomers, e.g., PEG20, PEG30, PEG40, PEG60, PEG80, PEG100, PEG115, PEG 200, PEG 300, PEG400, PEG500, PEG600, PEG 1000, PEG1500, PEG2000, PEG 3350, PEG4000, PEG4600, PEG5000, PEG6000, PEG8000, PEG11000, PEG12000, PEG2000000 and any mixtures thereof.

An "excipient" or a "carrier" means a component or an ingredient that is acceptable in the sense of being compatible with the other ingredients of compositions or formulations as disclosed herein and not overly deleterious to the patient or animal to which the formulation is to be administered. As used here, excipients and carriers include liquids, including benzyl benzoate, cottonseed oil, N,N-dimethylacetamide, a C_{2-12} alcohol (e.g., ethanol), glycerol, peanut oil, a PEG, vitamin E, poppyseed oil, propylene glycol, safflower oil, sesame oil, soybean oil and vegetable oil.

Excipients, as used herein may exclude solvents such as olive oil, chloroform, dioxane or DMSO. Excipients comprise one or more components typically used in the pharmaceutical formulation arts, e.g., fillers, binders, disintegrants and lubricants.

Unless otherwise specified, expressions that refer to "a formula 1 compound(s)", a "compound of the invention", a "formula 2A or 2B compound", a "plasma concentration-enhancing compound" and the like mean compositions or methods, e.g., methods to treat a togavirus infection as disclosed herein, where one or more than one formula 1 or formula 2A or 2B compound is present, typically 1, 2, 3 or 4, usually 1.

"Alcohol" as used herein, includes excipients, means an alcohol that comprises a C_{1-12} alkyl moiety substituted at one or more hydrogen atoms with one or more hydroxyl groups, usually one, two or three. Alcohols include, e.g., ethanol, *n*-propanol, *i*-propanol, *n*-butanol, *i*-butanol, *s*-butanol, *t*-butanol, *n*-pentanol, *i*-pentanol, *n*-hexanol, cyclohexanol, *n*-heptanol, *n*-octanol, *n*-nonanol, *n*-decanol and benzyl alcohol. The carbon atoms in alcohols can be straight, branched or cyclic. Alcohol includes any subset of the foregoing, e.g., C_{2-4} alcohols (alcohols having 2, 3 or 4 carbon atoms).

"Ester" means a moiety that comprises a -C(O)-O- structure. Typically, esters as used here comprise an organic moiety containing about 1-50 carbon atoms (e.g., about 2-12 carbon atoms) and 0 to about 10 independently selected heteroatoms (e.g., O, S, N, P, Si), where the organic moiety is bonded to a formula 1 steroid nucleus at R^2 through the -C(O)-O- structure, e.g., organic moiety-C(O)-O-steroid or organic moiety-O-C(O)-steroid. The organic moiety usually comprises one or more of any of the organic groups described above, e.g., C_{1-20} alkyl moieties, C_{2-20} alkenyl moieties, C_{2-20} alkynyl moieties, aryl moieties, C_{2-9} heterocycles or substituted derivatives of any of these, e.g., comprising 1, 2, 3, 4 or more substituents, where each substituent is independently chosen. Typical substitutions for hydrogen or carbon atoms in these organic groups include 1, 2, 3, 4 or more, usually 1, 2, or 3 -O-, -S-, $-NR^{PR}-$ (including -NH-), -C(O)-, =O, =S, $-N(R^{PR})_2$ (including $-NH_2$), $-C(O)OR^{PR}$ (including -C(O)OH), $-OC(O)R^{PR}$ (including -O-C(O)-H), $-OR^{PR}$ (including -OH), $-SR^{PR}$ (including -SH), $-NO_2$, -CN, -NHC(O)-, -C(O)NH-, -OC(O)-, -C(O)O-, -O-A8, -S-A8, -C(O)-A8, -OC(O)-A8, -C(O)O-A8, =N-, -N=, =N-OH, $-OPO_3(R^{PR})_2$, $-OSO_3H_2$ or halogen moieties or atoms, where each R^{PR} is -H, an independently selected protecting group or both R^{PR} together comprise a protecting group, and A8 is C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-4} alkyl-aryl (e.g., benzyl), aryl (e.g. phenyl) or C_{0-4} alkyl-C_{2-9} heterocycle. Substitutions are independently chosen. The organic moiety includes compounds defined by the R_4 variable. The organic moieties exclude obviously unstable moieties, e.g., -O-O-, except where such unstable moieties are transient species that one can use to make a compound with sufficient chemical stability for the one or more of the uses described herein. The substitutions listed above are typically substituents that one can use to replace one or more carbon atoms, e.g., -O- or -C(O)-, or one or more hydrogen atom, e.g., halogen, $-NH_2$, -OH or =O.

"Thioester" means a moiety that comprises a -C(S)-O- structure. Typically, thioesters as used here comprise an organic moiety containing about 1-50 carbon atoms (e.g., about 2-12 carbon atoms) and 0 to about 10 heteroatoms (e.g., O, S, N, P, Si), where the organic moiety is bonded to a formula 1 steroid nucleus at R^2 through the -C(S)-O- structure, e.g., organic moiety-C(S)-O-steroid or organic moiety-O-C(S)-steroid. The organic moiety usually comprises one or more of any of the organic groups described above, e.g., C_{1-20} alkyl moieties, C_{2-20} alkenyl moieties, C_{2-20} alkynyl moieties, aryl moieties, C_{2-9} heterocycles or substituted derivatives of any of these, e.g., comprising 1, 2, 3, 4 or more substituents, where each substituent is independently chosen. Typical substitutions for hydrogen or carbon atoms in these organic groups include 1, 2, 3, 4 or more, usually 1, 2, or 3 -O-, -S-, $-NR^{PR}-$ (including -NH-), -C(O)-, =O, =S, $-N(R^{PR})_2$ (including $-NH_2$), $-C(O)OR^{PR}$ (including -C(O)OH), $-OC(O)R^{PR}$ (including -O-C(O)-H), $-OR^{PR}$ (including -OH), $-SR^{PR}$ (including -SH), $-NO_2$, -CN, -NHC(O)-, -C(O)NH-, -OC(O)-, -C(O)O-, -O-A8, -S-A8, -C(O)-A8, -OC(O)-A8, -C(O)O-A8, =N-, -N=, =N-OH, $-OPO_3(R^{PR})_2$, $-OSO_3H_2$ or halogen moieties or atoms, where each R^{PR} is -H, an independently selected protecting group or both R^{PR} together comprise a protecting group, and A8 is C_{1-8} alkyl, C_{1-8} alkenyl, C_{1-8} alkynyl, C_{1-4} alkyl-aryl (e.g., benzyl), aryl (e.g. phenyl) or C_{0-4} alkyl-C_{2-9} heterocycle. Substitutions are independently chosen. The organic moiety includes compounds defined by the R_4 variable. The organic moieties exclude obviously unstable moieties, e.g., -O-O-, except where such unstable moieties are transient species that one can use to make a compound with sufficient chemical stability for the one or more of the uses described herein. The substitutions listed above are typically substituents that one can use to replace one or more carbon atoms, e.g., -O- or -C(O)-, or one or more hydrogen atom, e.g., halogen, $-NH_2$ or -OH.

"Thioacetal" means a moiety that comprises a -C(O)-S- structure. Typically, thioacetals as used here comprise an organic moiety containing about 1-50 carbon atoms (e.g., about 2-12 carbon atoms) and 0 to about 10 heteroatoms (e.g., O, S, N, P, Si), where the organic moiety is bonded to a formula 1 steroid nucleus at R^2 through the -C(O)-S- structure, e.g., organic moiety-C(O)-S-steroid or organic moiety-S-C(O)-steroid. The organic moiety is as described above for thioesters.

"Carbamate" means an organic moiety as described for ester that comprises 1, 2, 3, 4 or more $-O-C(O)NR^{PR}-$ structures where R^{PR} is -H, a protecting group or an organic moiety as described for ester. Typically, carbamate groups as used here comprise an organic moiety containing about 1-50 carbon atoms (e.g., about 2-12 carbon atoms) and 0 to about 10 heteroatoms (e.g., O, S, N, P, Si), where the organic moiety is bonded to a formula 1 steroid nucleus at R^2 through the $-O-C(O)-NR^{PR}-$ structure, e.g., organic moiety-NR^{PR}-C(O)-O-steroid or organic moiety-O-C(O)-NR^{PR}-steroid. The organic moiety is as described above for thioesters.

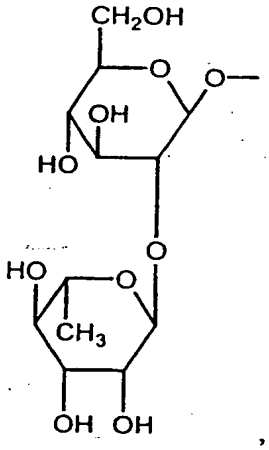
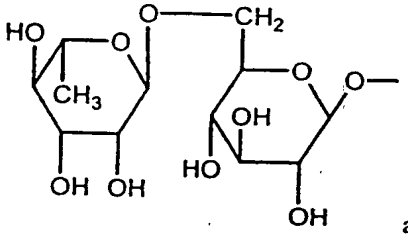
"Sulfate ester" means a moiety that comprises a -O-S(O)(O)-O- structure. Typically, sulfate esters as used here comprise an organic moiety containing about 1-50 carbon atoms (e.g., about 2-12 carbon atoms) and 0 to about 10 heteroatoms (e.g., O, S, N, P, Si), where the organic

moiety is bonded to a formula 1 steroid nucleus at R^2 through the -O-S(O)(O)-O- structure, e.g., organic moiety-O-S(O)(O)-O-steroid. The organic moiety is as described above for thioesters.

"Sulfite ester" means a moiety that comprises a -O-S(O)-O- structure. Typically, sulfite esters as used here comprise an organic moiety containing about 1-50 carbon atoms (e.g., about 2-12 carbon atoms) and 0 to about 10 heteroatoms (e.g., O, S, N, P, Si), where the organic moiety is bonded to a formula 1 steroid nucleus at R^2 through the -O-S(O)-O- structure, e.g., organic moiety-O-S(O)-O-steroid. The organic moiety is as described above for thioesters.

The compositions disclosed herein optionally comprise salts of the formula 1 and 2 compounds that comprise an ionizable moiety or a polar moiety. As used herein, "salts" include complexes that comprise moieties of opposite charge. Ionizable moieties include -O-S(O)(O)-OH or an $-NH_2$ group at R_2 and polar moieties include -OH. Salts include pharmaceutically acceptable salts that comprise, for example, an uncharged moiety or a monovalent anion moiety or a monovalent cation moiety. Salts include compounds derived by combination of appropriate anions such as inorganic acids. Suitable acids include those having sufficient acidity to form a stable salt, preferably acids of low toxicity. For example, one may form invention salts from acid addition of certain inorganic acids, e.g., HF, HCl, HBr, HI, H_2SO_4, H_3PO_4, to basic centers, typically amines that may be present in formula 1, 2A or 2B compounds. Or one may use certain organic acids, e.g., organic sulfonic acids, organic carboxylic acids in the same manner. Exemplary organic sulfonic acids include C_{6-16} aryl sulfonic acids, C_{6-16} heteroaryl sulfonic acids and C_{1-16} alkyl sulfonic acids such as phenyl, α-naphthyl, β-naphthyl, (*S*)-camphor, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *s*-butyl, *i*-butyl, *t*-butyl, pentyl and hexyl sulfonic acids. Exemplary organic carboxylic acids include C_{1-16} alkyl, C_{6-16} aryl carboxylic acids and C_{4-16} heteroaryl carboxylic acids such as acetic, glycolic, lactic, pyruvic, malonic, glutaric, tartaric, citric, fumaric, succinic, malic, maleic, hydroxymaleic, benzoic, hydroxybenzoic, phenylacetic, cinnamic, salicylic and 2-phenoxybenzoic. Salts also include the invention compound salts with one or more amino acids. Many amino acids are suitable, especially the naturally occurring amino acids found as protein components, although the amino acid typically is one bearing a side chain with a basic or acidic group, e.g., lysine, arginine or glutamic acid, or a neutral group such as glycine, serine, threonine, alanine, isoleucine, or leucine. Salts are usually biologically compatible or pharmaceutically acceptable or non-toxic, particularly for mammalian cells. Salts that are biologically toxic are generally used as synthetic intermediates for making other invention compounds.

The neohesperidoside, rutinoside and glucoside groups have the structures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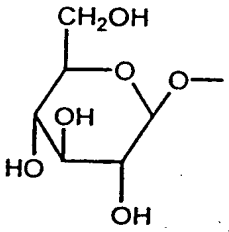

, respectively

wherein one or more of the hydrogen atoms are optionally independently substituted with hydroxy, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, glucuronide or a C_{1-25} fatty acid.

Heterocycle. "Heterocycle" or "heterocyclic" includes by way of example and not limitation these heterocycles described in Paquette, Leo A.; "Principles of Modern Heterocyclic Chemistry" (W. A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and *J. Am. Chem. Soc.* 1960, 82:5566; and U.S. patent 5763483, all of which are incorporated herein by reference.

Examples of heterocycles include by way of example and not limitation pyridyl, thiazolyl, tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2dithiazinyl, thienyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathinyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, 1H-indazoly, purinyl, 4H-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, and isatinoyl.

By way of example and not limitation, carbon bonded heterocycles are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine,

position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Still more typically, carbon bonded heterocycles include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl.

By way of example and not limitation, nitrogen bonded heterocycles are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β-carboline. Typically, nitrogen bonded heterocycles include 1-aziridyl, 1-azetedyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

"Heteroaryl" means an aromatic ring or two or more fused rings that contain one or more aromatic rings where the ring or fused rings comprise 1, 2, 3 or more heteroatoms, usually oxygen (-O-), nitrogen (-NX-) or sulfur (-S-) where X is -H, a protecting group or C_{1-6} alkyl, usually -H. Examples are as described for heterocycle.

Protecting groups. Various groups that the formula 1, 2A or 2B compounds may comprise include, e.g., substituted alkyl groups, substituted alkenyl groups, esters or substituted heterocycles, which can contain one or more reactive moieties such as hydroxyl, or thiol. Intermediates used to make formula 1 or formula 2A or 2B compounds may be protected as is apparent in the art. Noncyclic and cyclic protecting groups and corresponding cleavage reactions are described in "Protective Groups in Organic Chemistry", Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991, ISBN 0-471-62301-6) (hereafter "Greene"). In the context of the present invention, these protecting groups are groups that can be removed from the molecule of the invention without irreversibly changing the covalent bond structure or oxidation/reduction state of the remainder of the molecule. For example, the protecting group, -X, that is bonded to a -OX or -NHX group can be removed to form -OH or $-NH_2$, respectively, without affecting other covalent bonds in the molecule. At times, when desired, more than one protecting group can be removed at a time, or they can be removed sequentially. In compounds of the invention containing more than one protecting group, the protecting groups are the same or different.

Protecting groups are intended to be removed by known procedures, although it will be understood that the protected intermediates fall within the scope of this invention. The removal of the protecting group may be arduous or straightforward, depending upon the economics and nature of the conversions involved. In general, one will use a protecting group with exocyclic amines or with carboxyl groups during synthesis of a formula 1 compound. For most therapeutic applications amine groups should be deprotected. Protecting groups commonly are employed to protect against covalent modification of a sensitive group in reactions such as alkylation or acylation. Ordinarily, protecting groups are removed by, e.g. hydrolysis, elimination or aminolysis. Thus, simple

functional considerations will suffice to guide the selection of a reversible or an irreversible protecting group at a given locus on the invention compounds. Suitable protecting groups and criteria for their selection are described in T.W. Greene and P.G.M. Wuts, Eds. "Protective Groups in Organic Synthesis" 2nd edition, Wiley Press, at pps. 10-142, 143-174, 175-223, 224-276, 277-308, 309-405 and 406-454, which is incorporated herein by reference.

Determination of whether a group is a protecting group is made in the conventional manner, e.g., as illustrated by Kocienski, Philip J.; "*Protecting Groups*" (Georg Thieme Verlag Stuttgart, New York, 1994) (hereafter "Kocienski"), Section 1.1, page 2, and Greene Chapter 1, pages 1-9; and U.S. patent 5763483, all of which are incorporated herein by reference. In particular, a group is a protecting group if when, based on mole ratio, 90% of that protecting group has been removed by a deprotection reaction, no more than 50%, preferably 25%, more preferably 10%, of the deprotected product molecules of the invention have undergone changes to their covalent bond structure or oxidation/reduction state other than those occasioned by the removal of the protecting group. When multiple protecting groups of the same type are present in the molecule, the mole ratios are determined when all of the groups of that type are removed. When multiple protecting groups of different types are present in the molecule, each type of protecting group is treated (and the mole ratios are determined) independently or together with others depending on whether the deprotection reaction conditions pertinent to one type are also pertinent to the other types present. In one embodiment of the invention, a group is a protecting group if when, based on mole ratio determined by conventional techniques, 90% of that protecting group has been removed by a conventional deprotection reaction, no more than 50%, preferably 25%, more preferably 10%, of the deprotected product molecules of the invention have undergone irreversible changes to their covalent bond structure or oxidation/reduction state other than those occasioned by the removal of the protecting group. Irreversible changes require chemical reactions (beyond those resulting from aqueous hydrolysis, acid/base neutralization or conventional separation, isolation or purification) to restore the covalent bond structure or oxidation/reduction state of the deprotected molecule of the invention.

Protecting groups are also described in detail together with general concepts and specific strategies for their use in Kocienski, Philip J.; "Protecting Groups" (Georg Thieme Verlag Stuttgart, New York, 1994), which is incorporated by reference in its entirety herein. In particular Chapter 1, Protecting Groups: An Overview, pages 1-20, Chapter 2, Hydroxyl Protecting Groups, pages 21-94, Chapter 3, Diol Protecting Groups, pages 95-117, Chapter 4, Carboxyl Protecting Groups, pages 118-154, Chapter 5, Carbonyl Protecting Groups, pages 155-184, Chapter 6, Amino Protecting Groups, pages 185-243, Chapter 7, Epilog, pages 244-252, and Index, pages 253-260, are incorporated with specificity in the context of their contents. More particularly, Sections 2.3 Silyl Ethers, 2.4 Alkyl Ethers, 2.5 Alkoxyalkyl Ethers (Acetals), 2.6 Reviews (hydroxy and thiol protecting groups), 3.2 Acetals, 3.3 Silylene Derivatives, 3.4 1,1,3,3-Tetraisopropyldisiloxanylidene

Derivatives, 3.5 Reviews (diol protecting groups), 4.2 Esters, 4.3 2,6,7-Trioxabicyclo[2.2.2]octanes [OBO] and Other Ortho Esters, 4.4 Oxazolines, 4.5 Reviews (carboxyl protecting groups), 5.2 O,O-Acetals, 5.3 S,S-Acetals, 5.4 O,S-Acetals, 5.5 Reviews (carbonyl protecting groups), 6.2 N-Acyl Derivatives, 6.3 N-Sulfonyl Derivatives, 6.4 N-Sulfenyl Derivatives, 6.5 N-Alkyl Derivatives, 6.6 N-Silyl Derivatives, 6.7 Imine Derivatives, and 6.8 Reviews (amino protecting groups), are each incorporated with specificity where protection/deprotection of the requisite functionalities is discussed. Further still, the tables "Index to the Principal Protecting Groups" appearing on the inside front cover and facing page, "Abbreviations" at page xiv, and "reagents and Solvents" at page xv are each incorporated herein at this location.

Typical hydroxy protecting groups are described in Greene at pages 14-118 and include Ethers (Methyl); Substituted Methyl Ethers (Methoxymethyl, Methylthiomethyl, t-Butylthiomethyl, (Phenyldimethylsilyl)methoxymethyl, Benzyloxymethyl, p-Methoxybenzyloxymethyl, (4-Methoxyphenoxy)methyl, Guaiacolmethyl, t-Butoxymethyl, 4-Pentenyloxymethyl, Siloxymethyl, 2-Methoxyethoxymethyl, 2,2,2-Trichloroethoxymethyl, Bis(2-chloroethoxy)methyl, 2-(Trimethylsilyl)ethoxymethyl, Tetrahydropyranyl, 3-Bromotetrahydropyranyl, Tetrahydropthiopyranyl, 1-Methoxycyclohexyl, 4-methoxytetrahydropyranyl, 4-Methoxytetrahydrothiopyranyl, 4-Methoxytetrahydropthiopyranyl S,S-Dioxido, 1-[(2-Chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl, 1,4-Dioxan-2-yl, Tetrahydrofuranyl, Tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a-Octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl); Substituted Ethyl Ethers (1-Ethoxyethyl, 1-(2-Chloroethoxy)ethyl, 1-Methyl-1-methoxyethyl, 1-Methyl-1-benzyloxyethyl, 1-Methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-Trichloroethyl, 2-Trimethylsilylethyl, 2-(Phenylselenyl)ethyl, t-Butyl, Allyl, p-Chlorophenyl, p-Methoxyphenyl, 2,4-Dinitrophenyl, Benzyl); Substituted Benzyl Ethers (p-Methoxybenzyl, 3,4-Dimethoxybenzyl, o-Nitrobenzyl, p-Nitrobenzyl, p-Halobenzyl, 2,6-Dichlorobenzyl, p-Cyanobenzyl, p-Phenylbenzyl, 2- and 4-Picolyl, 3-Methyl-2-picolyl N-Oxido, Diphenylmethyl, p, p'-Dinitrobenzhydryl, 5-Dibenzosuberyl, Triphenylmethyl, alpha-Naphthyldiphenylmethyl, p-methoxyphenyldiphenylmethyl, Di(p-methoxyphenyl)phenylmethyl, Tri(p-methoxyphenyl)methyl, 4-(4'-Bromophenacyloxy)phenyldiphenylmethyl, 4,4', 4"-Tris(4,5-dichlorophthalimidophenyl)methyl, 4,4', 4"-Tris(levulinoyloxyphenyl)methyl, 4,4', 4"-Tris(benzoyloxyphenyl)methyl, 3-(Imidazol-1-ylmethyl)bis(4', 4"-dimethoxyphenyl)methyl, 1,1-Bis(4-methoxyphenyl)-1'-pyrenylmethyl, 9-Anthryl, 9-(9-Phenyl)xanthenyl, 9-(9-Phenyl-10-oxo)anthryl, 1,3-Benzodithiolan-2-yl, Benzisothiazolyl S,S-Dioxido); Silyl Ethers (Trimethylsilyl, Triethylsilyl, Triisopropylsilyl, Dimethylisopropylsilyl, Diethylisopropylsily, Dimethylthexylsilyl, t-Butyldimethylsilyl, t-Butyldiphenylsilyl, Tribenzylsilyl, Tri-p-xylylsilyl, Triphenylsilyl, Diphenylmethylsilyl, t-Butylmethoxyphenylsilyl); Esters (Formate, Benzoylformate, Acetate, Choroacetate, Dichloroacetate, Trichloroacetate, Trifluoroacetate, Methoxyacetate, Triphenylmethoxyacetate, Phenoxyacetate, p-Chlorophenoxyacetate, p-poly-Phenylacetate, 3-

Phenylpropionate, 4-Oxopentanoate (Levulinate), 4,4-(Ethylenedithio)pentanoate, Pivaloate, Adamantoate, Crotonate, 4-Methoxycrotonate, Benzoate, p-Phenylbenzoate, 2,4,6-Trimethylbenzoate (Mesitoate); Carbonates (Methyl, 9-Fluorenylmethyl, Ethyl, 2,2,2-Trichloroethyl, 2-(Trimethylsilyl)ethyl, 2-(Phenylsulfonyl)ethyl, 2-(Triphenylphosphonio)ethyl, Isobutyl, Vinyl, Allyl, p-Nitrophenyl, Benzyl, p-Methoxybenzyl, 3,4-Dimethoxybenzyl, o-Nitrobenzyl, p-Nitrobenzyl, S-Benzyl Thiocarbonate, 4-Ethoxy-1-naphthyl, Methyl Dithiocarbonate); Groups With Assisted Cleavage (2-Iodobenzoate, 4-Azidobutyrate, 4-Nitro-4-methylpentanoate, o-(Dibromomethyl)benzoate, 2-Formylbenzenesulfonate, 2-(Methylthiomethoxy)ethyl Carbonate, 4-(Methylthiomethoxy)butyrate, 2-(Methylthiomethoxymethyl)benzoate); Miscellaneous Esters (2,6-Dichloro-4-methylphenoxyacetate, 2,6-Dichloro-4-(1,1,3,3-tetramethylbutyl)phenoxyacetate, 2,4-Bis(1,1-dimethylpropyl)phenoxyacetate, Chorodiphenylacetate, Isobutyrate, Monosuccinoate, (E)-2-Methyl-2-butenoate (Tigloate), o-(Methoxycarbonyl)benzoate, p-poly-Benzoate, α-Naphthoate, Nitrate, Alkyl N,N,N', N'-Tetramethylphosphorodiamidate, N-Phenylcarbamate, Borate, Dimethylphosphinothioyl, 2,4-Dinitrophenylsulfenate); and Sulfonates (Sulfate, Methanesulfonate (Mesylate), Benzylsulfonate, Tosylate).

More typically hydroxy protecting groups include subtituted methyl ethers, substituted benzyl ethers, silyl ethers, and esters including sulfonic acid esters, still more typically, trialkylsilyl ethers, tosylates and acetates.

Typical 1,2- and 1,3-diol protecting groups are described in Greene at pages 118-142 and include Cyclic Acetals and Ketals (Methylene, Ethylidene, 1-t-Butylethylidene, 1-Phenylethylidene, (4-Methoxyphenyl)ethylidene, 2,2,2-Trichloroethylidene, Acetonide (Isopropylidene), Cyclopentylidene, Cyclohexylidene, Cycloheptylidene, Benzylidene, p-Methoxybenzylidene, 2,4-Dimethoxybenzylidene, 3,4-Dimethoxybenzylidene, 2-Nitrobenzylidene); Cyclic Ortho Esters (Methoxymethylene, Ethoxymethylene, Dimethoxymethylene, 1-Methoxyethylidene, 1-Ethoxyethylidine, 1,2-Dimethoxyethylidene, alpha-Methoxybenzylidene, 1-(N,N-Dimethylamino)ethylidene Derivative, alpha-(N,N-Dimethylamino)benzylidene Derivative, 2-Oxacyclopentylidene); and Silyl Derivatives (Di-t-butylsilylene Group, 1,3-(1,1,3,3-Tetraisopropyldisiloxanylidene) Derivative, Tetra-t-butoxydisiloxane-1,3-diylidene Derivative, Cyclic Carbonates, Cyclic Boronates, Ethyl Boronate, Phenyl Boronate).

More typically, 1,2- and 1,3-diol protecting groups include epoxides and acetonides.

Typical amino protecting groups are described in Greene at pages 315-385 and include Carbamates (Methyl and Ethyl, 9-Fluorenylmethyl, 9(2-Sulfo)fluoroenylmethyl, 9-(2,7-Dibromo)fluorenylmethyl, 2,7-Di-t-buthyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl, 4-Methoxyphenacyl); Substituted Ethyl (2,2,2-Trichoroethyl, 2-Trimethylsilylethyl, 2-Phenylethyl, 1-(1-Adamantyl)-1-methylethyl, 1,1-Dimethyl-2-haloethyl, 1,1-Dimethyl-2,2-dibromoethyl, 1,1-Dimethyl-2,2,2-trichloroethyl, 1-Methyl-1-(4-biphenylyl)ethyl, 1-

(3,5-Di-t-butylphenyl)-1-methylethyl, 2-(2'- and 4'-Pyridyl)ethyl, 2-(N,N-Dicyclohexylcarboxamido)ethyl, t-Butyl, 1-Adamantyl, Vinyl, Allyl, 1-Isopropylallyl, Cinnamyl, 4-Nitrocinnamyl, 8-Quinolyl, N-Hydroxypiperidinyl, Alkyldithio, Benzyl, p-Methoxybenzyl, p-Nitrobenzyl, p-Bromobenzyl, p-Chorobenzyl, 2,4-Dichlorobenzyl, 4-Methylsulfinylbenzyl, 9-Anthrylmethyl, Diphenylmethyl); Groups With Assisted Cleavage (2-Methylthioethyl, 2-Methylsulfonylethyl, 2-(p-Toluenesulfonyl)ethyl, [2-(1,3-Dithianyl)]methyl, 4-Methylthiophenyl, 2,4-Dimethylthiophenyl, 2-Phosphonioethyl, 2-Triphenylphosphonioisopropyl, 1,1-Dimethyl-2-cyanoethyl, m-Choro-p-acyloxybenzyl, p-(Dihydroxyboryl)benzyl, 5-Benzisoxazolylmethyl, 2-(Trifluoromethyl)-6-chromonylmethyl); Groups Capable of Photolytic Cleavage (m-Nitrophenyl, 3,5-Dimethoxybenzyl, o-Nitrobenzyl, 3,4-Dimethoxy-6-nitrobenzyl, Phenyl(o-nitrophenyl)methyl); Urea-Type Derivatives (Phenothiazinyl-(10)-carbonyl Derivative, N'-p-Toluenesulfonylaminocarbonyl, N'-Phenylaminothiocarbonyl); Miscellaneous Carbamates (t-Amyl, S-Benzyl Thiocarbamate, p-Cyanobenzyl, Cyclobutyl, Cyclohexyl, Cyclopentyl, Cyclopropylmethyl, p-Decyloxybenzyl, Diisopropylmethyl, 2,2-Dimethoxycarbonylvinyl, o-(N,N-Dimethylcarboxamido)benzyl, 1,1-Dimethyl-3-(N,N-dimethylcarboxamido)propyl, 1,1-Dimethylpropynyl, Di(2-pyridyl)methyl, 2-Furanylmethyl, 2-Iodoethyl, Isobornyl, Isobutyl, Isonicotinyl, p-(p'-Methoxyphenylazo)benzyl, 1-Methylcyclobutyl, 1-Methylcyclohexyl, 1-Methyl-1-cyclopropylmethyl, 1-Methyl-1-(3,5-dimethoxyphenyl)ethyl, 1-Methyl-1-(p-phenylazophenyl)ethyl, 1-Methyl-1-phenylethyl, 1-Methyl-1-(4-pyridyl)ethyl, Phenyl, p-(Phenylazo)benzyl, 2,4,6-Tri-t-butylphenyl, 4-(Trimethylammonium)benzyl, 2,4,6-Trimethylbenzyl); Amides (N-Formyl, N-Acetyl, N-Choroacetyl, N-Trichoroacetyl, N-Trifluoroacetyl, N-Phenylacetyl, N-3-Phenylpropionyl, N-Picolinoyl, N-3-Pyridylcarboxamide, N-Benzoylphenylalanyl Derivative, N-Benzoyl, N-p-Phenylbenzoyl); Amides With Assisted Cleavage (N-o-Nitrophenylacetyl, N-o-Nitrophenoxyacetyl, N-Acetoacetyl, (N'-Dithiobenzyloxycarbonylamino)acetyl, N-3-(p-Hydroxyphenyl)propionyl, N-3-(o-Nitrophenyl)propionyl, N-2-Methyl-2-(o-nitrophenoxy)propionyl, N-2-Methyl-2-(o-phenylazophenoxy)propionyl, N-4-Chlorobutyryl, N-3-Methyl-3-nitrobutyryl, N-o-Nitrocinnamoyl, N-Acetylmethionine Derivative, N-o-Nitrobenzoyl, N-o-(Benzoyloxymethyl)benzoyl, 4,5-Diphenyl-3-oxazolin-2-one); Cyclic Imide Derivatives (N-Phthalimide, N-Dithiasuccinoyl, N-2,3-Diphenylmaleoyl, N-2,5-Dimethylpyrrolyl, N-1,1,4,4-Tetramethyldisilylazacyclopentane Adduct, 5-Substituted 1,3-Dimethyl-1,3,5-triazacyclohexan-2-one, 5-Substituted 1,3-Dibenzyl-1,3,5-triazacyclohexan-2-one, 1-Substituted 3,5-Dinitro-4-pyridonyl); N-Alkyl and N-Aryl Amines (N-Methyl, N-Allyl, N-[2-(Trimethylsilyl)ethoxy]methyl, N-3-Acetoxypropyl, N-(1-Isopropyl-4-nitro-2-oxo-3-pyrrolin-3-yl), Quaternary Ammonium Salts, N-Benzyl, N-Di(4-methoxyphenyl)methyl, N-5-Dibenzosuberyl, N-Triphenylmethyl, N-(4-Methoxyphenyl)diphenylmethyl, N-9-Phenylfluorenyl, N-2,7-Dichloro-9-fluorenylmethylene, N-Ferrocenylmethyl, N-2-Picolylamine N'-Oxide); Imine Derivatives (N-1,1-Dimethylthiomethylene, N-Benzylidene, N-p-

methoxybenylidene, N-Diphenylmethylene, N-[(2-Pyridyl)mesityl]methylene, N,(N',N'-Dimethylaminomethylene, N,N'-Isopropylidene, N-p-Nitrobenzylidene, N-Salicylidene, N-5-Chlorosalicylidene, N-(5-Chloro-2-hydroxyphenyl)phenylmethylene, N-Cyclohexylidene); Enamine Derivative (N-(5,5-Dimethyl-3-oxo-1-cyclohexenyl)); N-Metal Derivatives (N-Borane Derivatives, N-Diphenylborinic Acid Derivative, N-[Phenyl(pentacarbonylchromium- or -tungsten)]carbenyl, N-Copper or N-Zinc Chelate); N-N Derivatives (N-Nitro, N-Nitroso, N-Oxide); N-P Derivatives (N-Diphenylphosphinyl, N-Dimethylthiophosphinyl, N-Diphenylthiophosphinyl, N-Dialkyl Phosphoryl, N-Dibenzyl Phosphoryl, N-Diphenyl Phosphoryl); N-Si Derivatives; N-S Derivatives; N-Sulfenyl Derivatives (N-Benzenesulfenyl, N-o-Nitrobenzenesulfenyl, N-2,4-Dinitrobenzenesulfenyl, N-Pentachlorobenzenesulfenyl, N-2-nitro-4-methoxybenzenesulfenyl, N-Triphenylmethylsulfenyl, N-3-Nitropyridinesulfenyl); andN-Sulfonyl Derivatives (N-p-Toluenesulfonyl, N-Benzenesulfonyl, N-2,3,6-Trimethyl-4-methoxybenzenesulfonyl, N-2,4,6-Trimethoxybenzenesulfonyl, N-2,6-Dimethyl-4-methoxybenzenesulfonyl, N-Pentamethylbenzenesulfonyl, N-2,3,5,6,-Tetramethyl-4-methoxybenzenesulfonyl, N-4-methoxybenzenesulfonyl, N-2,4,6- Trimethylbenzenesulfonyl, N-2,6-Dimethoxy-4-methylbenzenesulfonyl, N-2,2,5,7,8-Pentamethylchroman-6-sulfonyl, N-Methanesulfonyl, N-.beta.-Trimethylsilyethanesulfonyl, N-9-Anthracenesulfonyl, N-4-(4', 8'-Dimethoxynaphthylmethyl)benzenesulfonyl, N-Benzylsulfonyl, N-Trifluoromethylsulfonyl, N-Phenacylsulfonyl).

More typically, amino protecting groups include carbamates and amides, still more typically, N-acetyl groups.

Stereoisomers. The formula 1 and formula 2A or 2B compounds include enriched or resolved optical isomers at any or all asymmetric atoms as are apparent from the depictions. Both racemic and diasteromeric mixtures, as well as the individual optical isomers can be isolated or synthesized so as to be substantially free of their enantiomeric or diastereomeric partners, and these are all within the scope of the invention. Chiral centers may be found in invention compounds at, for example, R^1, R^2 or R^4.

One or more of the following methods are used to prepare the enantiomerically enriched or pure isomers herein. The methods are listed in approximately their order of preference, i.e.; one ordinarily should employ stereospecific synthesis from chiral precursors before chromatographic resolution before spontaneous crystallization.

Stereospecific synthesis is described in the examples. Methods of this type conveniently are used when the appropriate chiral starting material is available and reaction steps are chosen that do not result in undesired racemization at chiral sites. One advantage of stereospecific synthesis is that it does not produce undesired enantiomers that must be removed from the final product, thereby lowering overall synthetic yield. In general, those skilled in the art would understand what starting

materials and reaction conditions should be used to obtain the desired enantiomerically enriched or pure isomers by stereospecific synthesis.

If a suitable stereospecific synthesis cannot be empirically designed or determined with routine experimentation then those skilled in the art would turn to other methods. One method of general utility is chromatographic resolution of enantiomers on chiral chromatography resins. These resins are packed in columns, commonly called Pirkle columns, and are commercially available. The columns contain a chiral stationary phase. The racemate is placed in solution and loaded onto the column, and thereafter separated by HPLC. See for example, Proceedings Chromatographic Society - International Symposium on Chiral Separations, Sept. 3-4, 1987, which is incorporated herein by reference. Examples of chiral columns that could be used to screen for the optimal separation technique would include Diacel Chriacel OD, Regis Pirkle Covalent D-phenylglycine, Regis Pirkle Type 1A, Astec Cyclobond II, Astec Cyclobond III, Serva Chiral D-DL=Daltosil 100, Bakerbond DNBLeu, Sumipax OA-1000, Merck Cellulose Triacetate column, Astec Cyclobond I-Beta, or Regis Pirkle Covalent D-Naphthylalanine. Not all of these columns are likely to be effective with every racemic mixture. However, those skilled in the art understand that a certain amount of routine screening may be required to identify the most effective stationary phase. When using such columns it is desirable to employ embodiments of the compounds of this invention in which the charges are not neutralized, e.g., where acidic functionalities such as carboxyl are not esterified or amidated.

Another method entails converting the enantiomers in the mixture to diasteriomers with chiral auxiliaries and then separating the conjugates by ordinary column chromatography. This is a very suitable method, particularly when the embodiment contains a free hydroxyl that will form a salt or covalent bond to a chiral auxiliary. Chirally pure amino acids, organic acids or organosulfonic acids are all worthwhile exploring as chiral auxiliaries, all of which are well known in the art. Salts with such auxiliaries can be formed, or they can be covalently (but reversibly) bonded to the functional group.

Enzymatic resolution is another method of potential value. In such methods one prepares covalent derivatives of the enantiomers in the racemic mixture, generally lower alkyl esters, and then exposes the derivative to enzymatic cleavage, generally hydrolysis. For this method to be successful an enzyme must be chosen that is capable of stereospecific cleavage, so it is frequently necessary to routinely screen several enzymes. If esters are to be cleaved, then one selects a group of esterases, phosphatases, and lipases and determines their activity on the derivative. Typical esterases are from liver, pancreas or other animal organs, and include porcine liver esterase.

If the enantiomeric mixture separates from solution or a melt as a conglomerate, i.e., a mixture of enantiomerically pure crystals, then the crystals can be mechanically separated, thereby producing the enantiomerically enriched preparation. This method, however, is not practical for large-scale preparations and is of limited value for true racemic compounds.

Asymmetric synthesis is another technique for achieving enantiomeric enrichment. For example, a chiral protecting group is reacted with the group to be protected and the reaction mixture allowed to equilibrate. If the reaction is enantiomerically specific then the product will be enriched in that enantiomer.

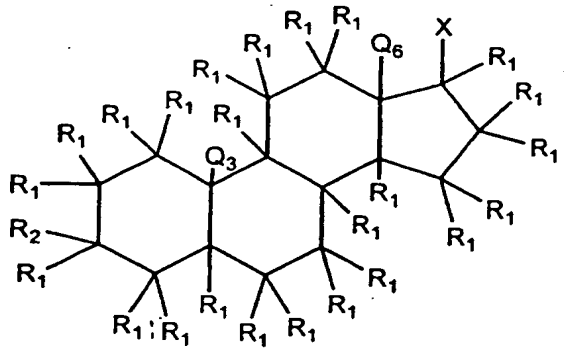
Further guidance in the separation of enantiomeric mixtures can be found, by way of example and not limitation, in "Enantiomers, Racemates, and resolutions", Jean Jacques, Andre Collet, and Samuel H. Wilen (Krieger Publishing Company, Malabar, FL, 1991, ISBN 0-89464-618-4): Part 2, Resolution of Enantiomer Mixture, pages 217-435; more particularly, section 4, Resolution by Direct Crystallization, pages 217-251, section 5, Formation and Separation of Diastereomers, pages 251-369, section 6, Crystallization-Induced Asymmetric Transformations, pages 369-378, and section 7, Experimental Aspects and Art of Resolutions, pages 378-435; still more particularly, section 5.1.4, Resolution of Alcohols, Transformation of Alcohols into Salt-Forming Derivatives, pages 263-266, section 5.2.3, Covalent Derivatives of Alcohols, Thiols, and Phenols, pages 332-335, section 5.1.1, Resolution of Acids, pages 257-259, section 5.1.2, Resolution of Bases, pages 259-260, section 5.1.3, Resolution of Amino Acids, page 261-263, section 5.2.1, Covalent Derivatives of Acids, page 329, section 5.2.2, Covalent derivatives of Amines, pages 330-331, section 5.2.4, Covalent Derivatives of Aldehydes, Ketones, and Sulfoxides, pages 335-339, and section 5.2.7, Chromatographic Behavior of Covalent Diastereomers, pages 348-354, all of which are incorporated herein by reference.

Embodiments include compositions that transiently occur when a method step or operation is performed. For example, when a formula 1 compound is contacted with an excipient, e.g., water, a cyclodextrin, a PEG, an alcohol, propylene glycol, benzyl alcohol or benzyl benzoate, the composition before addition of one ingredient with another is a non-homogenous mixture. As the ingredients are contacted, the mixture's homogeneity increases and the proportion of ingredients relative to each other approaches a desired value. Thus, some compositions as disclosed herein, optionally contain less than about 3% w/w water, e.g., less than 0.5% w/w water, can comprise about 0.0001-99% w/w of a formula 1 compound such as 16α-bromoepiandrosterone and one or more excipients. These transient compositions are intermediates that necessarily arise when one makes an invention composition or formulation and they are included in invention embodiments to the extent that they are patentable.

Formula 1 compounds. The formula 1 compounds, or the "compounds of the invention", are useful to treat a subject having, or prevent infection of a subject with, one or more togaviruses. Togaviruses, as used herein includes the *Togaviridae* family, including the *Alphavirus* and *Rubivirus* genera, as well as the flavivirus family (*Flaviviridae*) and the *Flavivirus* and *Pestivirus* genera. A review of virus taxonomy and the biology of these viruses may be found at, e.g., B.N. Fields, et al., editors, *Fundamental Virology*, 3rd edition, 1996, Lippencott-Raven Publishers, chapter 1 (pages 15-58) and chapter 17 (pages 523-540), which is incorporated herein by reference.

For preferred formula 1 compounds, the R_2 moiety bonded to the steroid ring is generally in the β configuration, two R_1 are bonded to Q_2 and X is a double bonded oxygen moiety (=O). Typically, one of the R_1 bonded to Q_2 is hydrogen in the β configuration, the other R_1 bonded to Q_2 is hydrogen or a halogen, usually bromine, in the α configuration and a double bond is present at the 5-6 positions. Such preferred compounds include dehydroepiandrosterone ("DHEA") and 16α-bromodehydroepiandrosterone ("Br-DHEA").

Other preferred formula 1 compounds include 17-ketosteriods of formula 1 where a double bond is present at the 5-6 positions, X is =O, Q_2 is $-CH_2-$ or -CHBr-, R_2 is -H, -S(O)(O)-OH, -S(O)(O)-ONa, $-S(O)(O)-O-CH_2-CH(O-C(O)-R_6)-CH_2-O-C(O)-R_6$ (where R6 independently is C_{1-14} straight or branched alkyl), $-P(O)(O)-O-CH_2-CH(O-C(O)R_7)-CH_2-O-C(O)-R_7$ (where R_7 independently is a glucuronide group or C_{1-14} straight or branched alkyl) or R2 is a glucuronide group. Other preferred compounds include compound having the structures 20-43



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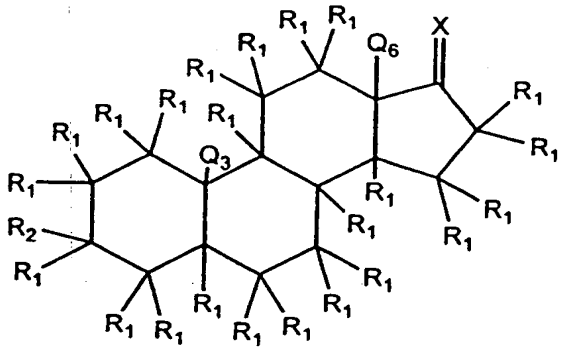

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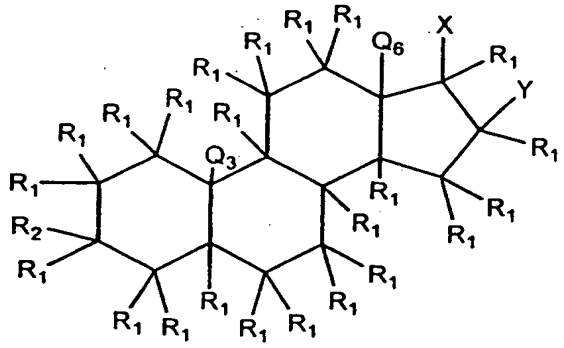

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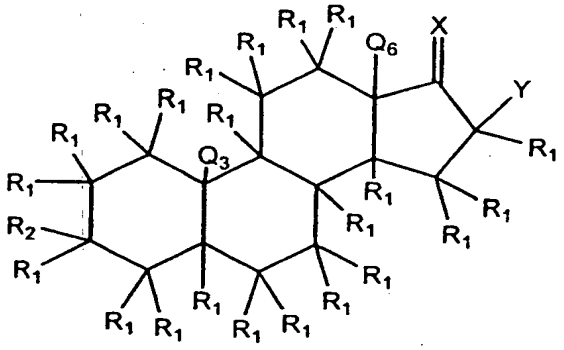

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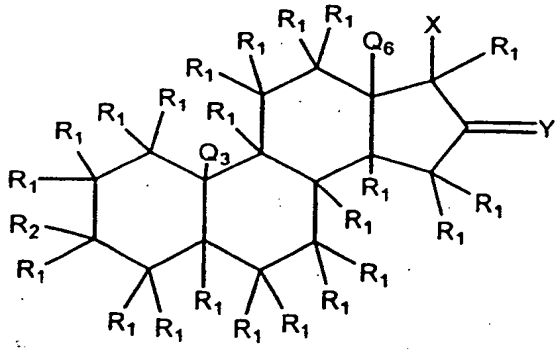

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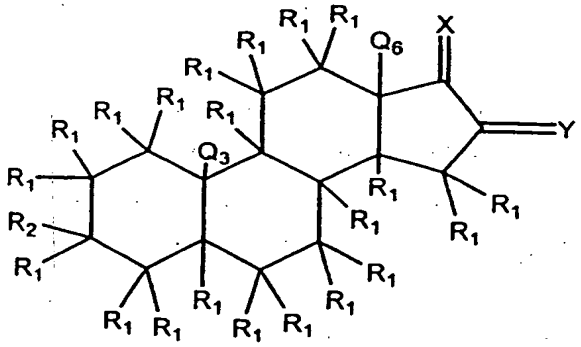

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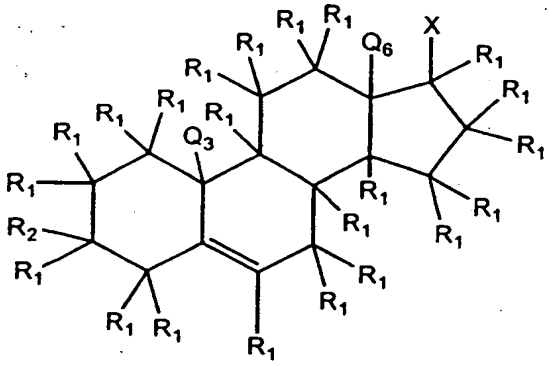

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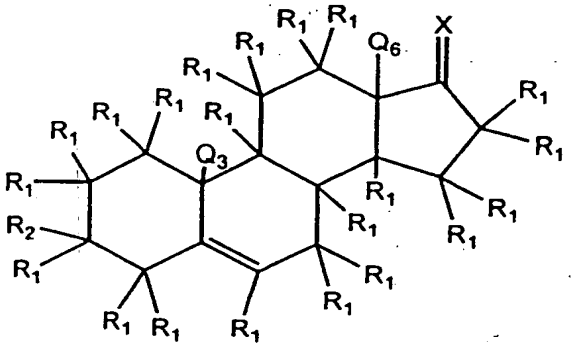

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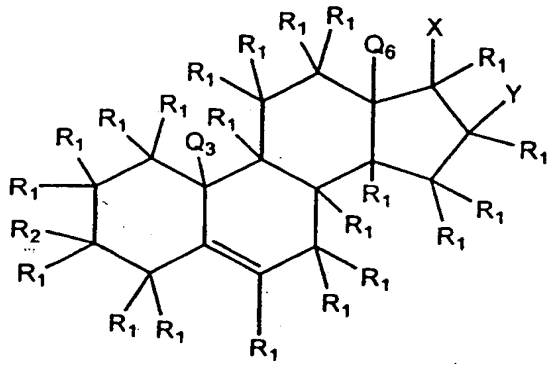

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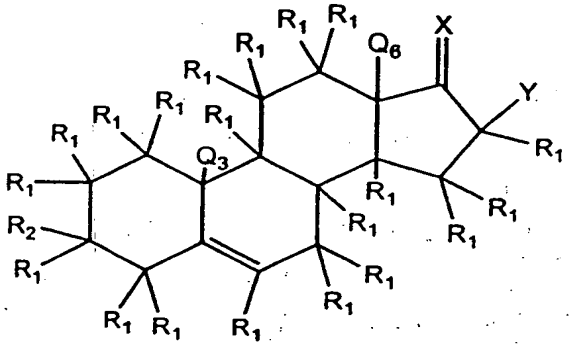

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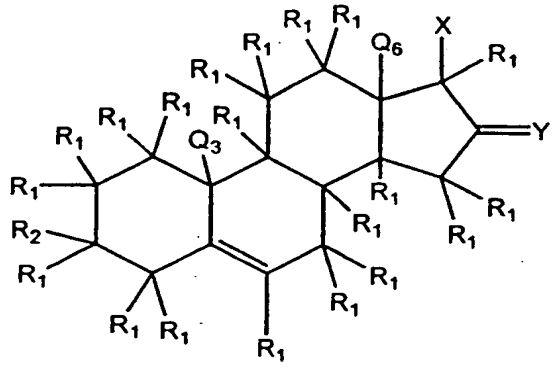

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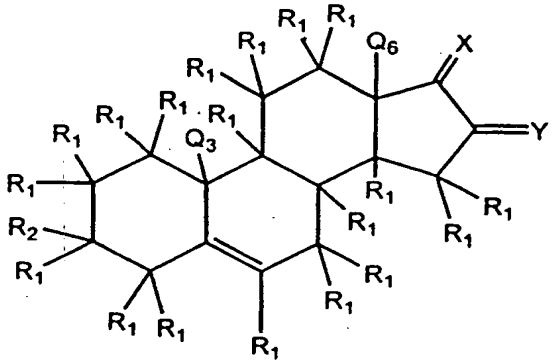

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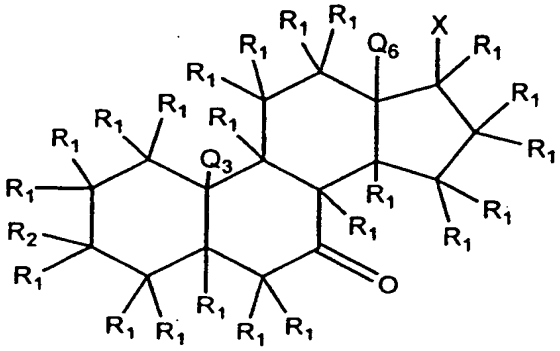

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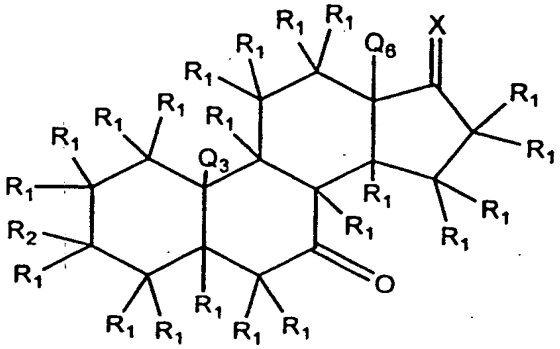

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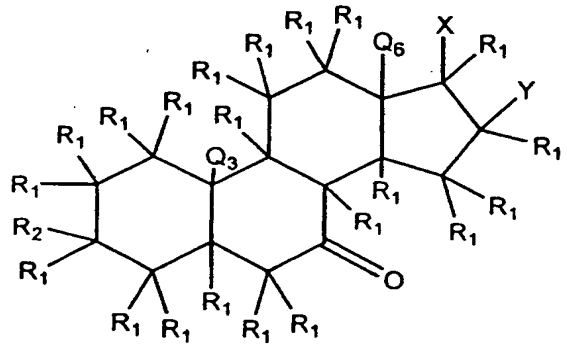

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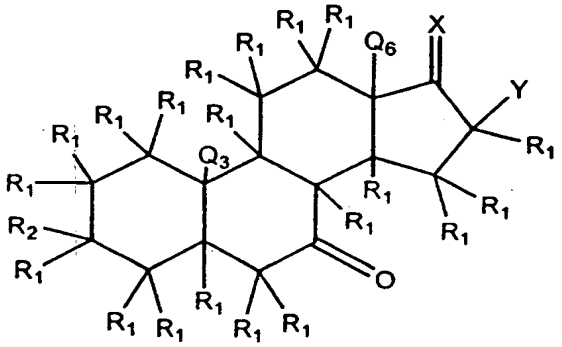

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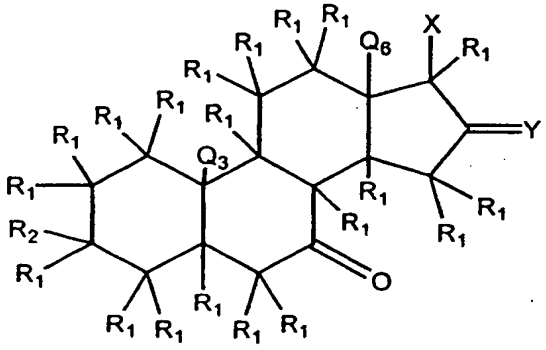

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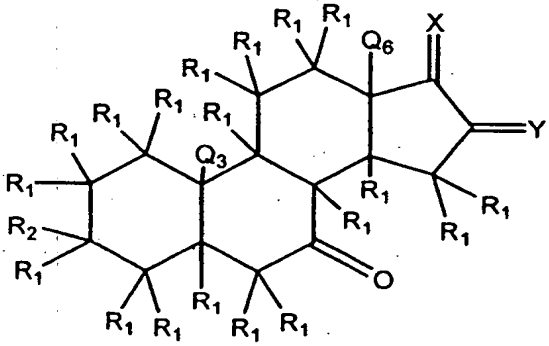

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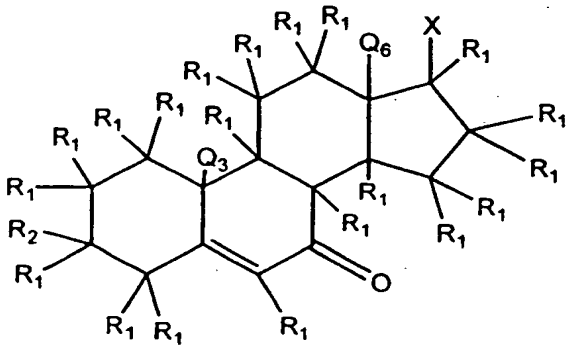

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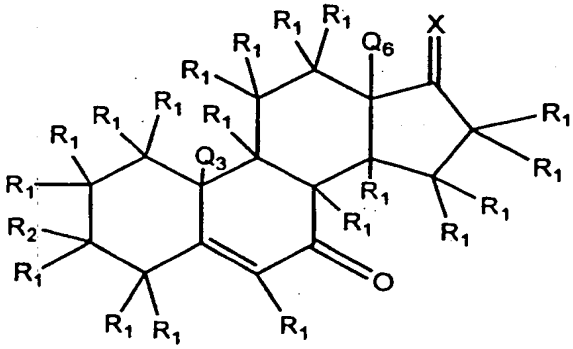

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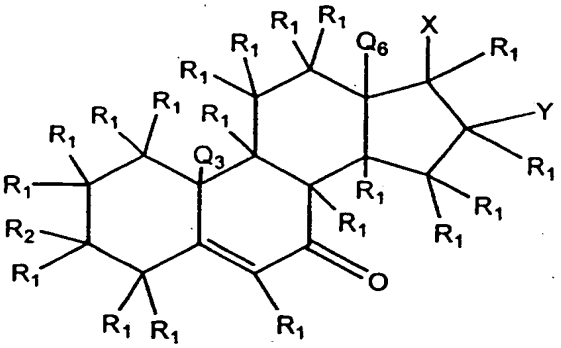

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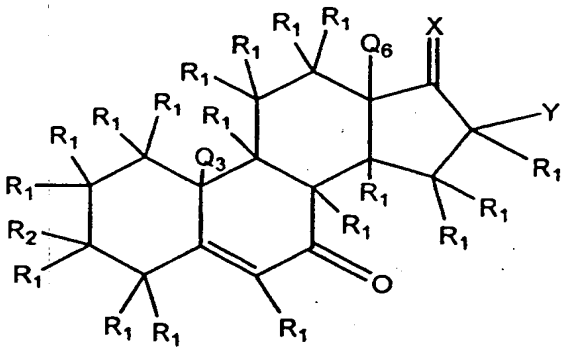

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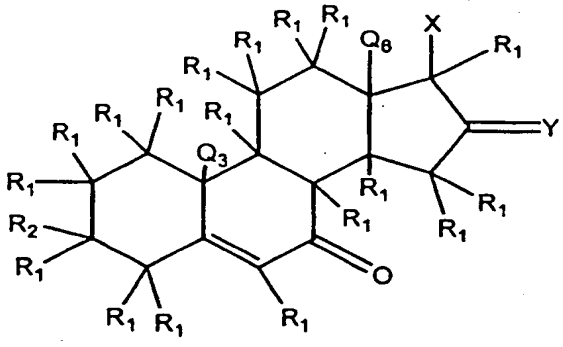
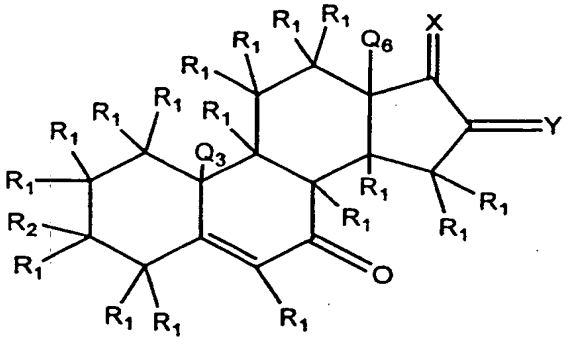




42 43

wherein for each of structures 20-43

Q_3 and Q_6 are each $-C(R_1)_3$ wherein each R_1 is independently selected;

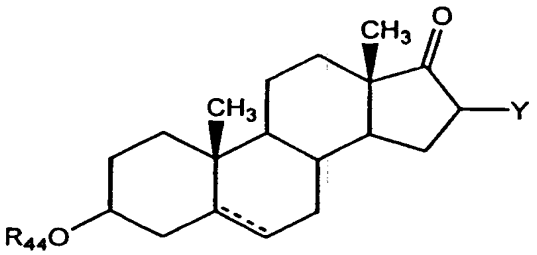
X and Y independently are -OH, -H, lower alkyl (e.g., C_{1-6} alkyl), $-C(O)-O-R_5$, $-O-C(O)-R_5$, halogen or, X and Y together with the R_1 at the same position independently are a ketone (=O);

each R_1 is independently selected and has the definition given above; and

R_2 has the definition given above.

In some embodiments, the formula 1 compound has the structure 20-43 and 2, 3, 4, 5 or 6 R_1 groups independently are -OH, halogen or alkoxy, and the remaining R_1 are all hydrogen; R_2 is -OH, an ester a thioester or a carbamate, or R_2, together with the R_1 at the 3-position comprises =O; Y is -H, -OH, a halogen or $-O-C(O)-R_5$, or Y, together with the R_1 at the 16-position comprises =O; X is -OH or $-O-C(O)-R_5$, or X, together with the R_1 at the 17-position comprises =O; and Q_3 and Q_6 independently are $-CH_3$ or $-CH_2OH$. Such embodiments include structure 20-43 compounds where two -OH are present at the 3-position, the 16-position or at the 17-position.

Preferred invention embodiments include compounds having the formula 44



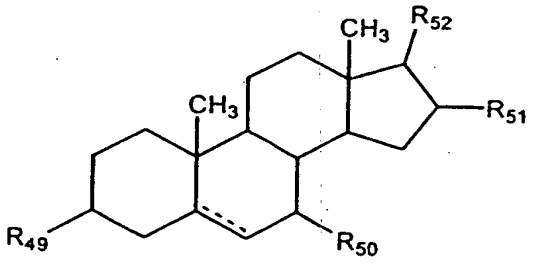
44

wherein Y is hydrogen or bromine, R_{44} is -H, -S(O)(O)-OH, -S(O)(O)-ONa, $-S(O)(O)-O-CH_2-CH(O-C(O)-R_6)-CH_2-O-C(O)-R_6$, $-P(O)(O)-O-CH_2-CH(O-C(O)-R_7)-CH_2-O-C(O)-R_7$ or a glucuronide group of structure (A). In other preferred embodiments, Y and R_{44} in formula 44 are both hydrogen. An especially preferred compound is dehydroepiandrosterone (Y and R_{44} in formula 44 are both hydrogen and the double bond at the 5-6 position is present). In other embodiments, the compound is epiandrosterone (Y and R_{44} in formula 44 are both hydrogen and the double bond at the 5-6 position is absent). A 16-haloepiandrosterone with a F, Cl, Br or I at the 16 position can also be used as an antiviral agent, e.g., 16α-bromoepiandrosterone. Other preferred compounds are (i) 16α-bromodehydroepiandrosterone, (ii) dehydroepiandrosterone-3-sulfate (Y is -H and R_{44} is -S(O)(O)-OM in formula 44 are both hydrogen and the double bond at the 5-6 position is present) and (iii) 5β-androstan-3β-ol-17-one. Related embodiments comprise compounds related to formula 44 compounds comprise the formula 44 compounds wherein 1, 2, 3, 4, 5 or 6 hydrogen atoms that are bonded to the steroid nucleus are substituted with independently selected -OH, -Br, -Cl, -F, -I, $-OCH_3$ or $-OC_2H_5$ atoms or groups.

In other embodiments, the 17-ketosteroids of formula 1 are dehydro-epiandrosterone where R_{44} in formula 44 is a $-S(O)(O)-O-CH_2-CH(O-C(O)-R_6)-CH_2-O-C(O)-R_5$, $-P(O)(O)-O-CH_2-CH(O-$

C(O)-R_7)-CH_2-O-C(O)-R_7 or a glucuronide group of structure (A), Y is hydrogen and the 5-6 double bond is present. Other formula 44 compounds include conjugates of dehydroepiandrosterone wherein Y is hydrogen, a double bond is present at the 5-6 position and R_{44} is hexyl sulfate, dodecyl sulfate, octadecyl sulfate, octadecanoyl sulfate, O-dihexadecylglycerol sulfate, hexadecane sulfonate, dioctadecanoylglycerol phosphate or O-hexadecylglycerol phosphate.

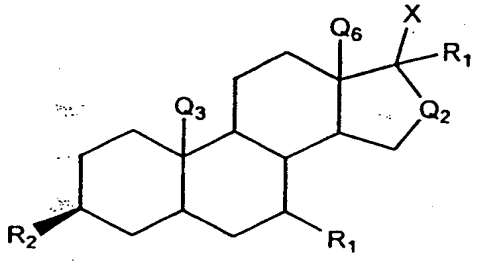
In another preferred aspect of the invention, the steroid of formula 1 is a compound of formula 45



45

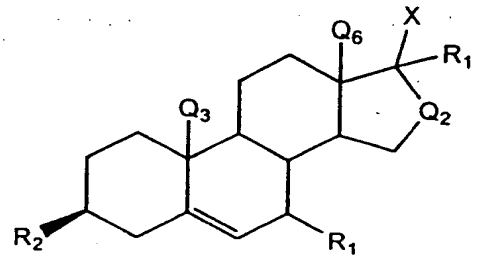
wherein R_{50} is -H, -OH or =O; R_{51} is -Br, -Cl, -F or -I; R_{52} is -OH or =O; R_{49} is -H, -OH, or -OR_{53}; and R_{53} is C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, a C_{1-18} ester, a C_{1-18} thioester, wherein any of the foregoing C_{1-18} or C_{2-18} groups is substituted at one or more hydrogen atoms with one or more independently selected -O-, -S-, -OH, -NH_2, -SH or =O groups or R_{53} is thioacetal, a sulfate ester, a sulfonate ester, a carbamate or a thioester. In one preferred aspect, R_{49} is -O-C(O)-CH_2-CH_2-$CH(R_{54})$-$CH(R_{55})$-CH_2R_{56} wherein R_{54} is -NH_2, -OH, -SH, -O-PO_3, -SO_3 or -OSO_3; R_{55} is -H, -NH_2, -OH, -SH, -O-PO_3, -SO_3 or -OSO_3; and R_{56} is C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, a C_{1-18} ester, a C_{1-18} thioester, wherein any of the foregoing C_{1-18} or C_{2-18} groups is substituted at one or more hydrogen atoms with one or more independently selected -OH, -NH_2, -SH or =O groups, and the precursors, metabolites and analogs thereof. Related embodiments comprise compounds related to formula 45 compounds wherein 1, 2, 3, 4, 5 or 6 hydrogen atoms that are bonded to the steroid nucleus are substituted with independently selected -OH, -Br, -Cl, -F, -I, -OCH_3 or -OC_2H_5 atoms or groups.

In other preferred embodiments, the formula 1 compounds have the formula 1B or 1C



1B

or



1C

wherein each R_1 independently is -H, -OH, a halogen, -$CHCH_2$, -$CHCHCH_3$, -CCH, -$CCCH_3$, or, or, the other moiety that is bonded to the same carbon atom is absent and R_1 is =O; R_2 is -H, -OH, a

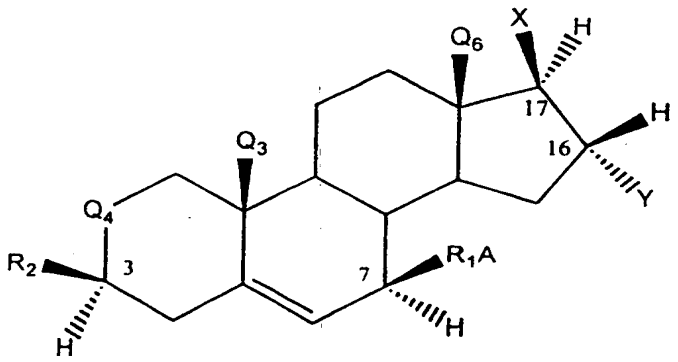
halogen, C_{1-8} alkoxy, -S-C(O)-$(CH_2)_m$-R_4, -C(O)-S-$(CH_2)_m$-R_4, -O-S(O)(O)-$(CH_2)_m$-R_4, -O-S(O)(O)-O-$(CH_2)_m$-R_4, -O-C(O)-NH-$(CH_2)_m$-R_4, -NH-C(O)-O-$(CH_2)_m$-R_4, -O-C(S)-$(CH_2)_m$-R_4, -C(S)-O-$(CH_2)_m$-R_4, -O-C(O)-$(CH_2)_m$-R_4 or -C(O)-O-$(CH_2)_m$-R_4; R_4 is -H, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-C_2H_4OH$, $-C_3H_6OH$, $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-O-CH_2-CH_3$, $-CH_2-CH_2-O-CH_2-CH_2OH$, a C_{3-6} alkenyl group, a C_{3-6} alkynyl group, benzyl or phenyl, wherein the phenyl or benzyl groups are optionally substituted with 1, 2, or 3 independently selected halogen, C_{1-4} alkoxy, -OH, -SH, -O- or -NH- moieties; and Q_3 and Q_6 independently are -H, $-CH_3$ or $-CH_2OH$; Q_2 is $-C(R_1)_2-$ or $-CH_2-CH_2-$; and m is 0, 1, 2 or 3. In these embodiments, Q_3 and Q_6 are usually both in the β-configuration, typically they are $-CH_3$, Q_2 usually comprises $-CH_2-$, -C(O)-, -CH(Br)-, -CH(I)-, or -CH(OH)- with the Br, I or OH moieties in the α-configuration, or Q_2 comprises =O, and R_1 at the 7-position is -H, -OH or =O. Related embodiments comprise compounds related to formula 1B and 1C compounds wherein 1, 2, 3, 4, 5 or 6 hydrogen atoms that are bonded to the steroid nucleus are substituted with independently selected -OH, -Br, -Cl, -F, -I, $-OCH_3$ or $-OC_2H_5$ atoms or groups.

The formula 1 compounds can exist in a crystalline or polymorphic form.

Metabolites. Also falling within the scope of this invention are the *in vivo* metabolites of the compounds of the invention, to the extent such products are novel and unobvious over the prior art. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered formula 1 compound, due to enzymatic or chemical processes. Accordingly, the invention includes novel and unobvious compounds produced by a process comprising contacting a compound of this invention with a subject, e.g., a human, rodent or a primate, for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled (e.g. C^{14} or H^3) compound of the invention, administering it parenterally or orally in a detectable dose (e.g. greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, primate, or to a human, allowing sufficient time for metabolism to occur (typically about 30 seconds to about 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, e.g. by HPLC, MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found *in vivo*, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention even if they possess no therapeutic activity of their own.

The following description exemplifies embodiments of the formula 1 compounds.

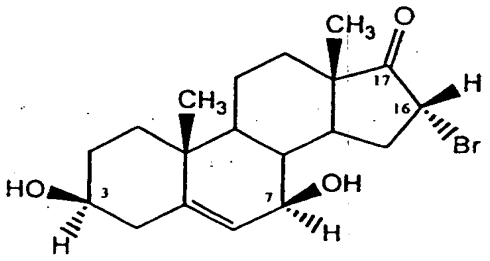
Group 1. Exemplary embodiments include the formula 1 compounds named in table B based on the compound structure designations defined in table A. Each compound named in Table B is depicted as a compound of formula 4



4

where Q_3 and Q_6 are both $-CH_3$, Q_4 is $-CH_2-$ and R_2, R_1A, and Y and X have the structures designated in Table A. The compounds named according to Tables A and B are referred to as "group 1" compounds.

Compounds named in Table B are designated by numbers assigned to R_2, R_1A, Y and X according to the following compound naming convention, $R_2.R_1A.Y.X$, using the numbered chemical structures depicted in Table A. As shown in formula 4, R_2 is in the 3β-position and hydrogen fills the remaining valence or R_2 is double bonded to the 3 carbon, R_1A is an R_1 group at the 7β-position or R_1A is an R_1 group double bonded to the 7 carbon, Y is in the 16α-position and hydrogen fills the remaining valence or R_2 is double bonded to the 16 carbon and X is in the 17β-position and hydrogen fills the remaining valence or X is double bonded to the 17 carbon. When R_2, R_1A, Y or X is a divalent moiety, e.g., =O, the hydrogen at the corresponding position is absent. Thus, the group 1 compound named 1.2.1.1 specifies a formula 4 structure with a β-hydroxyl bonded to carbons at the 3- and 7-positions (the variable groups R_2 and R_1A respectively), an α-bromine bonded to carbon 16 (the variable group Y) and double bonded oxygen (=O) at carbon 17 (the variable group X), i.e., having the structure shown below.



1.2.1.1

TABLE A

R2	R1A
1 -OH	1 -H
2 =O	2 -OH
3 -O-P(O)(O)-OH	3 =O
4 -O-P(O)(O)-O-CH_2-CH(O-C(O)-CH_3)-CH_2-O-C(O)CH_3	4 -CH_3
5 -O-S(O)(O)-OH	5 -OCH_3
6 -O-S(O)(O)-O$^-$$Na^+$	6 -OC_2H_5
7 -O-S(O)(O)-OC_2H_5	7 -$OCH_2CH_2CH_3$
8 -O-S(O)(O)-O-CH_2-CH(O-C(O)-CH_3)-CH_2-O-C(O)CH_3	8 -$OCH(CH_3)CH_3$
9 -O-S(O)(O)-$OCH_2CH_2CH_2CH_3$	9 -$OCH_2CH_2CH_2CH_3$
10 -O-S(O)(O)-$OC(CH_3)_3$	10 -$OC(CH_3)_3$

Y	X
1 -Br	1 =O
2 -Cl	2 -OH
3 -I	3 -H
4 -F	4 -F
5 -H	5 -Cl
6 -OH	6 -Br
7 =O	7 -I
8 -O-C(O)-CH_3	8 -O-C(O)-CH_3
9 -O-C(O)-CH_2CH_3	9 -O-C(O)-CH_2CH_3
10 -O-C(O)-$CH_2CH_2CH_3$	10 -O-C(O)-$CH_2CH_2CH_3$

TABLE B

1.1.1.1, 1.1.1.2, 1.1.1.3, 1.1.1.4, 1.1.1.5, 1.1.1.6, 1.1.1.7, 1.1.1.8, 1.1.1.9, 1.1.1.10, 1.1.2.1, 1.1.2.2, 1.1.2.3, 1.1.2.4, 1.1.2.5, 1.1.2.6, 1.1.2.7, 1.1.2.8, 1.1.2.9, 1.1.2.10, 1.1.3.1, 1.1.3.2, 1.1.3.3, 1.1.3.4, 1.1.3.5, 1.1.3.6, 1.1.3.7, 1.1.3.8, 1.1.3.9, 1.1.3.10, 1.1.4.1, 1.1.4.2, 1.1.4.3, 1.1.4.4, 1.1.4.5, 1.1.4.6, 1.1.4.7, 1.1.4.8, 1.1.4.9, 1.1.4.10, 1.1.5.1, 1.1.5.2, 1.1.5.3, 1.1.5.4, 1.1.5.5, 1.1.5.6, 1.1.5.7, 1.1.5.8, 1.1.5.9, 1.1.5.10, 1.1.6.1, 1.1.6.2, 1.1.6.3, 1.1.6.4, 1.1.6.5, 1.1.6.6, 1.1.6.7, 1.1.6.8, 1.1.6.9, 1.1.6.10, 1.1.7.1, 1.1.7.2, 1.1.7.3, 1.1.7.4, 1.1.7.5, 1.1.7.6, 1.1.7.7, 1.1.7.8, 1.1.7.9, 1.1.7.10, 1.1.8.1, 1.1.8.2, 1.1.8.3, 1.1.8.4, 1.1.8.5, 1.1.8.6, 1.1.8.7, 1.1.8.8, 1.1.8.9, 1.1.8.10, 1.1.9.1, 1.1.9.2, 1.1.9.3, 1.1.9.4, 1.1.9.5, 1.1.9.6, 1.1.9.7, 1.1.9.8, 1.1.9.9, 1.1.9.10, 1.1.10.1, 1.1.10.2, 1.1.10.3, 1.1.10.4, 1.1.10.5, 1.1.10.6, 1.1.10.7, 1.1.10.8, 1.1.10.9, 1.1.10.10, 1.2.1.1, 1.2.1.2, 1.2.1.3, 1.2.1.4, 1.2.1.5, 1.2.1.6, 1.2.1.7, 1.2.1.8, 1.2.1.9, 1.2.1.10, 1.2.2.1, 1.2.2.2, 1.2.2.3, 1.2.2.4, 1.2.2.5, 1.2.2.6, 1.2.2.7, 1.2.2.8,

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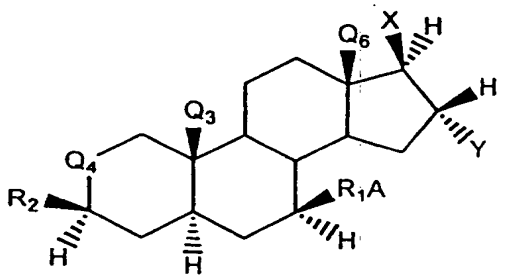
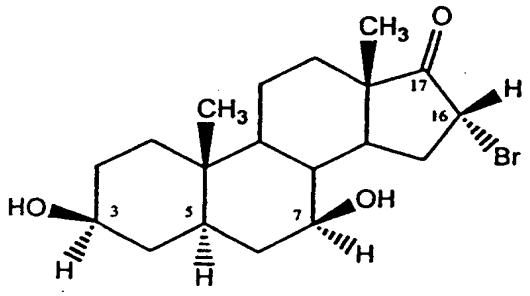
Additional exemplary formula I compound groups include the following groups as disclosed below.

Group 2. Group 2 compounds are as named in Table B, i.e., R_2, R_1A, Y and X substituents are as defined in Table A, but they are bonded to the steroid nucleus shown in formula 5, which is the same as the formula 4 steroid nucleus, except that the 5-6 double bond is absent and hydrogen is present at the 5-position in the α-configuration



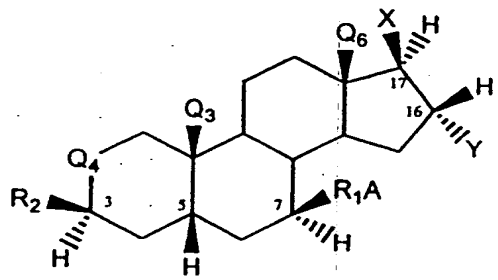
5.

Thus, the group 2 compound named 1.2.1.1 has the structure



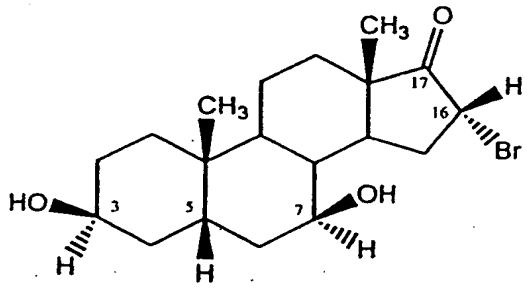
group 2, compound 1.2.1.1.

Group 3. Group 3 compounds are as named in Table B, i.e., R_2, R_1A, Y and X substituents are as defined in Table A, but they are bonded to the steroid nucleus shown in formula 6, which is the same as the formula 4 steroid nucleus, except that the 5-6 double bond is absent and hydrogen is present at the 5-position in the β-configuration



6.

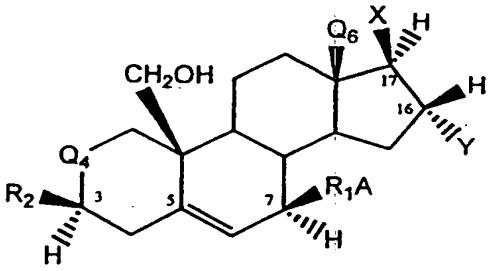
Thus, the group 3 compound named 1.2.1.1 has the structure



group 3, compound 1.2.1.1.

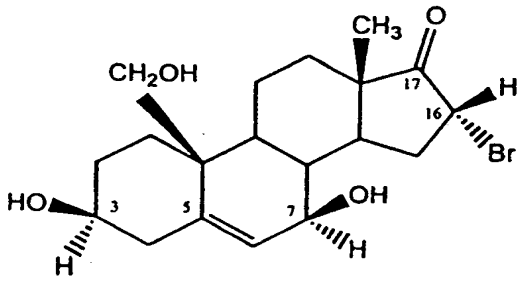
Group 4. Group 4 compounds are as named in Table B, i.e., R_2, R_1A, Y and X substituents are as defined in Table A, but they are bonded to the steroid nucleus shown in formula 7, which is the same as the formula 4 steroid nucleus, except that Q_3 is

$-CH_2OH$



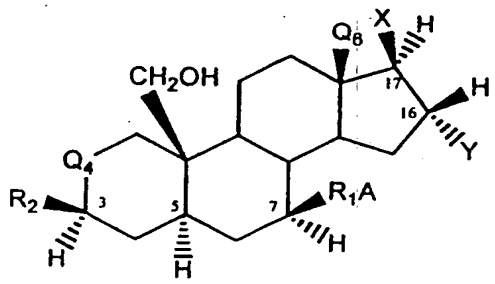
7.

Thus, the group 4 compound named 1.2.1.1 has the structure



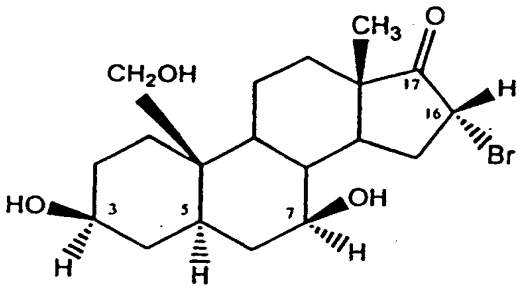
group 4, compound 1.2.1.1.

Group 5. Group 5 compounds are as named in Table B, i.e., R_2, R_1A, Y and X substituents are as defined in Table A, but they are bonded to the steroid nucleus shown in formula 8, which is the same as the formula 4 steroid nucleus, except that the 5-6 double bond is absent and hydrogen is present at the 5-position in the α-configuration and Q_3 is -CH_2OH



8.

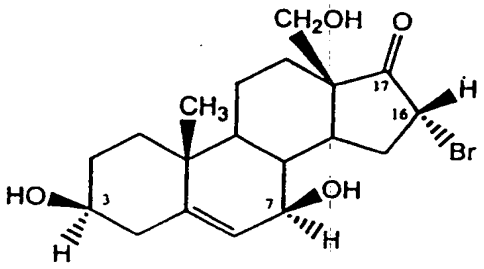
Thus, the group 5 compound named 1.2.1.1 has the structure



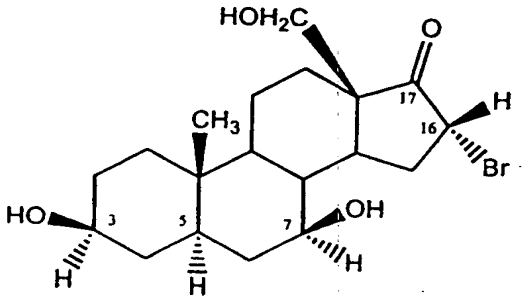
group 5, compound 1.2.1.1.

Group 6. Group 6 compounds are as named in groups 1-5, except that Q_6 in formulas 4-8 is -CH_2OH instead of methyl. In group 6, there are 5 subgroups of group 6 compounds. The first subgroup, subgroup 6-1, has the same steroid nucleus with the substituents as defined for group 1

compounds while the second, subgroup 6-2, has the same steroid nucleus with the substituents as defined for group 2 compounds. Subgroups 6-3 through 6-5 have the same steroid nucleus with the substituents as defined for group 3 through 5 respectively. Thus, for example, the subgroup 6-1 compound named 1.2.1.1 has the structure



and the subgroup 6-2 compound named 1.2.1.1 has the structure



Group 7. Group 7 compounds are as named in groups 1-5, except that the Y moiety in formulas 4-8 is in the β-configuration instead of in the α-configuration. Group 7 comprises 5 subgroups, wherein the compounds are named essentially as described for group 6 compounds, except that the Y group is in the β-configuration.

Group 8. Group 8 compounds are as named in groups 1-5, except that the X moiety in formulas 4-8 is in the α-configuration instead of in the β-configuration. Group 8 comprises 5 subgroups, wherein the compounds are named essentially as described for group 6 compounds, except that the X group is in the α-configuration.

Group 9. Group 9 compounds are as named in groups 1-5, except that the R_2 moiety in formulas 4-8 is in the α-configuration instead of in the β-configuration. Group 9 comprises 5 subgroups, wherein the compounds are named essentially as described for group 6 compounds, except that the R_2 group is in the α-configuration.

Group 10. Group 10 compounds are as named in groups 1-9, except that R_2 moieties 1 through 10 in Table A are replaced with the following moieties.

1 -S-C(O)-CH_3

2 -S-C(O)-CH_2-C_6H_5

3 -O-S(O)-O-CH_3

4 -O-S(O)-O-CH_2-C_6H_5

5 -O-S(O)(O)-O-CH_3

6 -O-S(O)(O)-O-CH_2-C_6H_5

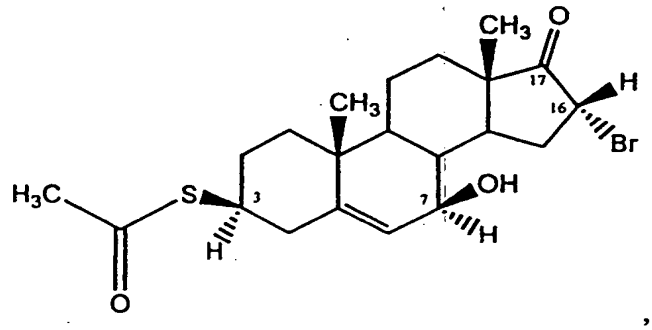
7 -O-C(O)-NH-CH_3

8 -O-C(O)-NH-C_6H_5

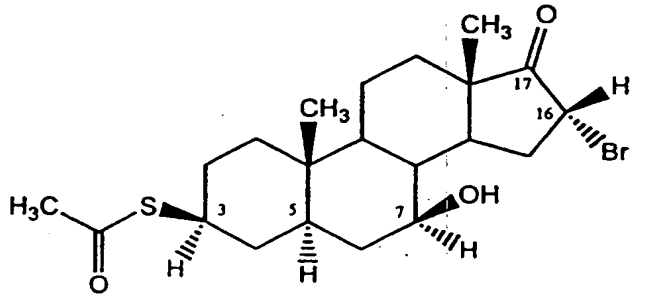
9 -O-C(S)-CH_3

10 -O-C(S)-CH_2-C_6H_5

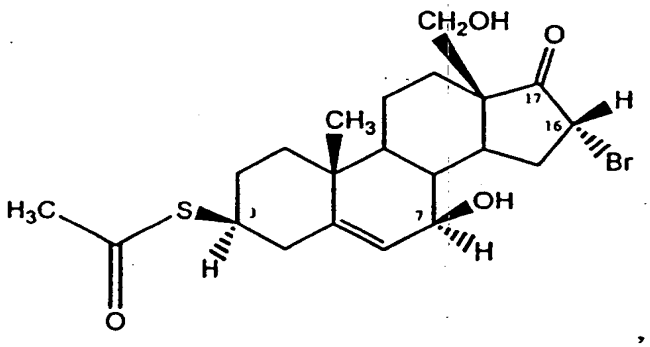
Group 10 comprises 25 subgroups of compounds. The first, subgroup 10-1, has the same steroid nucleus with substituents as defined for group 1, except that the R_2 moieties or groups listed replace those in Table A above. The subgroup 10-1 compound named 1.2.1.1 has the structure



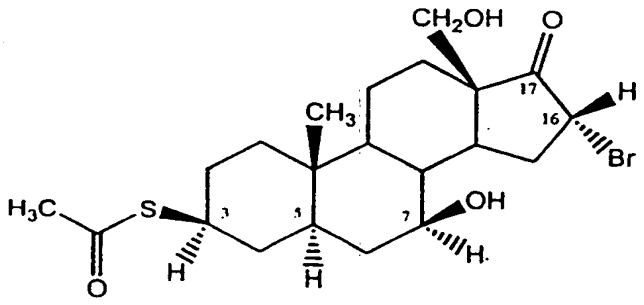
the subgroup 10-2 compound named 1.2.1.1 has the structure



the subgroup 10-6-1 compound named 1.2.1.1 has the structure



and the subgroup 10-6-2 compound named 1.2.1.1 has the structure



Group 11. Group 11 compounds are as named in groups 1-9, except that R_2 moieties 1 through 10 in Table A are replaced with the following moieties.

1 -S-C(O)-CH_2CH_2-O-CH_2CH_3

2 -S-C(O)-CH_2-$C_6H_4OCH_3$

3 -O-S(O)-O-CH_2CH_2-O-CH_2CH_3

4 -O-S(O)-O-CH_2-$C_6H_4OCH_3$

5 -O-S(O)(O)-O-CH_2CH_2-O-CH_2CH_3

6 -O-S(O)(O)-O-CH_2-$C_6H_4OCH_3$

7 -O-C(O)-NH-CH_2CH_2-O-CH_2CH_3

8 -O-C(O)-NH-$C_6H_4OCH_3$

9 -O-C(S)-CH_2CH_2-O-CH_2CH_3

10 -O-C(S)-CH_2-$C_6H_4OCH_3$

Group 11 comprises 25 subgroups, wherein the compounds are named essentially as described for group 10 compounds, except that the R_2 group is given above.

Group 12. Group 12 compounds are as named in groups 1-9, except that R_2 moieties 1 through 10 in Table A are replaced with the following moieties.

1 -S-C(O)-CH_2CH_2-O-CH_2C(O)OH

2 -S-C(O)-CH_2-C_6H_4F

3 -O-S(O)-O-CH_2CH_2-O-CH_2C(O)OH

4 -O-S(O)-O-CH_2-C_6H_4F

5 -O-S(O)(O)-O-CH_2CH_2-O-CH_2C(O)OH

6 -O-S(O)(O)-O-CH_2-C_6H_4F

7 -O-C(O)-NH-CH_2CH_2-O-CH_2C(O)OH

8 -O-C(O)-NH-C_6H_4F

9 -O-C(S)-CH_2CH_2-O-CH_2C(O)OH

10 -O-C(S)-CH_2-C_6H_4F

Group 13. Group 13 compounds are as named in groups 1-9, except that R_2 moieties 1 through 10 in Table A are replaced with the following moieties.

1 -S-C(O)-CH_2CH_2-O-CH_2CH_2OH

2 -S-C(O)-CH_2-$C_6H_4CH_3$

3 -O-S(O)-O-CH_2CH_2-O-CH_2CH_2OH

4 -O-S(O)-O-CH_2-$C_6H_4CH_3$

5 -O-S(O)(O)-O-CH_2CH_2-O-CH_2CH_2OH

6 -O-S(O)(O)-O-CH_2-$C_6H_4CH_3$

7 -O-C(O)-NH-CH_2CH_2-O-CH_2CH_2OH

8 -O-C(O)-NH-$C_6H_4CH_3$

9 -O-C(S)-CH_2CH_2-O-CH_2CH_2OH

10 -O-C(S)-CH_2-$C_6H_4CH_3$

Group 14. Group 14 compounds are as named in groups 1-9, except that R_2 moieties 1 through 10 in Table A are replaced with the following moieties.

1 -S-C(O)-CH_2CH_2-O-$CH_2CH_2OR^{PR}$

2 -S-C(O)-CH_2-$C_6H_4OR^{PR}$

3 -O-S(O)-O-CH_2CH_2-O-$CH_2CH_2OR^{PR}$

4 -O-S(O)-O-CH_2-$C_6H_4OR^{PR}$

5 -O-S(O)(O)-O-CH_2CH_2-O-$CH_2CH_2OR^{PR}$

6 -O-S(O)(O)-O-CH_2-$C_6H_4OR^{PR}$

7 -O-C(O)-NH-CH_2CH_2-O-$CH_2CH_2OR^{PR}$

8 -O-C(O)-NH-$C_6H_4OR^{PR}$

9 -O-C(S)-CH_2CH_2-O-$CH_2CH_2OR^{PR}$

10 -O-C(S)-CH_2-$C_6H_4OR^{PR}$

Group 15. Group 15 compounds are as named in groups 1-9, except that R_2 moieties 1 through 10 in Table A are replaced with the following moieties.

1 -S-C(O)-CH_2CH_2-O-$CH_2CH_2NHR^{PR}$

2 -S-C(O)-CH_2-$C_6H_3(OR^{PR})_2$

3 -O-S(O)-O-CH_2CH_2-O-$CH_2CH_2NHR^{PR}$

4 -O-S(O)-O-CH_2-$C_6H_3(OR^{PR})_2$

5 -O-S(O)(O)-O-CH_2CH_2-O-$CH_2CH_2NHR^{PR}$

6 -O-S(O)(O)-O-CH_2-$C_6H_3(OR^{PR})_2$

7 -O-C(O)-NH-CH_2CH_2-O-$CH_2CH_2NHR^{PR}$

8 -O-C(O)-NH-$C_6H_3(OR^{PR})_2$

9 -O-C(S)-CH_2CH_2-O-$CH_2CH_2NHR^{PR}$

10 -O-C(S)-CH_2-$C_6H_3(OR^{PR})_2$

Group 16. Group 16 compounds are as named in groups 1-9, except that R_2 moieties 1 through 10 in Table A are replaced with the following moieties.

1 -S-C(O)-$(CH_2)_{0-6}$-CH_3

2 -S-C(O)-CH_2-C_6H_5

3 -O-S(O)-O-$(CH_2)_{0-6}$-CH_3

4 -O-S(O)-O-CH_2-C_6H_5

5 -O-S(O)(O)-O-$(CH_2)_{0-6}$-CH_3

6 -O-S(O)(O)-O-CH_2-C_6H_5

7 -O-C(O)-NH-$(CH_2)_{0-6}$-CH_3

8 -O-C(O)-NH-$(CH_2)_{0-6}$-C_6H_5

9 -O-C(S)-$(CH_2)_{0-6}$-CH_3

10 -O-C(S)-CH_2-C_6H_5

Group 17. Group 17 compounds are as named in groups 1-9, except that R_2 moieties 1 through 10 in Table A are replaced with the following moieties.

1 -S-C(O)-CH_2CH_2-$(O$-$CH_2CH_2)_{1-50}$-H

2 -S-C(O)-CH_2-$C_6H_4OCH_3$

3 -O-S(O)-O-CH_2CH_2-$(O$-$CH_2CH_2)_{1-50}$-H

4 -O-S(O)-O-CH_2-$C_6H_4OCH_3$

5 -O-S(O)(O)-O-CH_2CH_2-$(O$-$CH_2CH_2)_{1-50}$-H

6 -O-S(O)(O)-O-CH_2-$C_6H_4OCH_3$

7 -O-C(O)-NH-CH_2CH_2-$(O$-$CH_2CH_2)_{1-50}$-H

8 -O-C(O)-NH-$C_6H_4OCH_3$

9 -O-C(S)-CH_2CH_2-$(O$-$CH_2CH_2)_{1-50}$-H

10 -O-C(S)-CH_2-$C_6H_4OCH_3$

Group 18. Group 18 compounds are as named in groups 1-9, except that R_2 moieties 1 through 10 in Table A are replaced with the following moieties.

1 -O-C(O)-CH_2CH_2-$(O$-$CH_2CH_2)_{1-50}$-H

2 -O-C(O)-CH_2-$C_6H_4OCH_3$

3 -O-C(O)-$(CH_2)_{0-6}$-CH_3

4 -O-C(O)-CH_2-$C_6H_4NO_2$

5 -O-C(O)-CH_2CH_2-$(O$-$CH_2CH_2)_{1-50}$-H

6 -O-C(O)-CH_2-C_6H_5

7 -O-C(O)-CH_2CH_2-O-CH_2CH_3

8 -O-C(O)-C_6H_5

9 -O-C(O)-CH_2CH_2-S-CH_2CH_3

10 -O-C(O)-CH_2-C_6H_4F

Group 19. Group 19 compounds are as named in groups 1-9, except that R_2 moieties 1 through 10 in Table A are replaced with the following moieties.

1 -O-CH_2CH_2-$(O$-$CH_2CH_2)_{1-50}$-H

2 -O-CH_2-$C_6H_4OCH_3$

3 -O-$(CH_2)_{0-6}$-CH_3

4 -O-CH_2-$C_6H_4NO_2$

5 -O-CH_2CH_2-(O-CH_2CH_2)$_{1-50}$-H

6 -O-CH_2-C_6H_5

7 -O-CH_2CH_2-O-CH_2CH_3

8 -O-C_6H_5

9 -O-CH_2CH_2-S-CH_2CH_3

10 -O-CH_2-C_6H_4F

Group 20. Group 20 compounds are as named in groups 1-9, except that R_2 moieties 1 through 10 in Table A are replaced with the following moieties.

1 -C(O)-O-CH_2CH_2-(O-CH_2CH_2)$_{1-50}$-H

2 -C(O)-O-CH_2-$C_6H_4OCH_3$

3 -C(O)-O-(CH_2)$_{0-6}$-CH_3

4 -C(O)-O-CH_2-$C_6H_4NO_2$

5 -C(O)-O-CH_2CH_2-(O-CH_2CH_2)$_{1-50}$-H

6 -C(O)-O-CH_2-C_6H_5

7 -C(O)-O-CH_2CH_2-O-CH_2CH_3

8 -C(O)-O-C_6H_5

9 -C(O)-O-CH_2CH_2-S-CH_2CH_3

10 -C(O)-O-CH_2-C_6H_4F

Group 21. Group 21 compounds are as named in groups 1-9, except that R_2 moieties 1 through 10 in Table A are replaced with the following moieties.

1 -C(O)-O-G12

2 -O-C(O)-G12

3 -C(O)-S-G12

4 -S-C(O)-G12

5 -C(S)-O-G12

6 -O-C(S)-G12

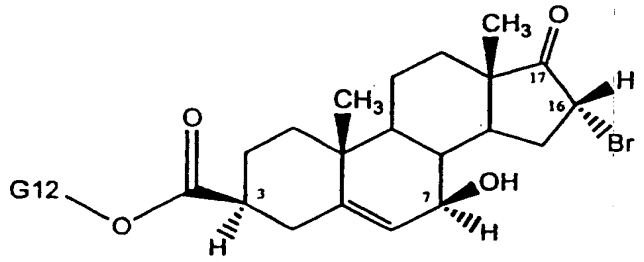
7 -O-C(O)-NH-G12

8 -NH-C(O)-O-G12

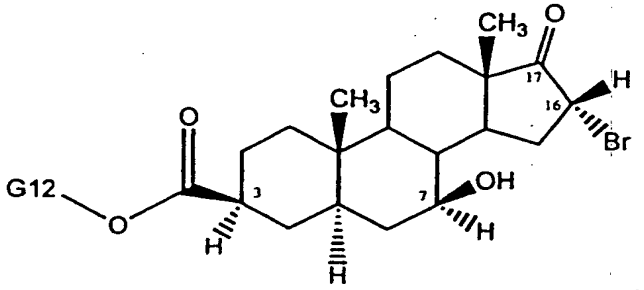
9 -C(O)-O-CH_2-G12

10 -O-C(O)-CH_2-G12

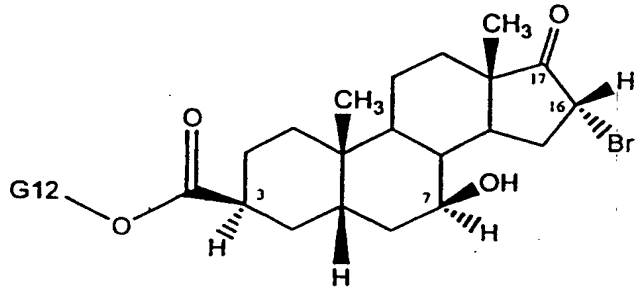
Thus, the group 21-1 compound named 1.2.1.1 has the structure



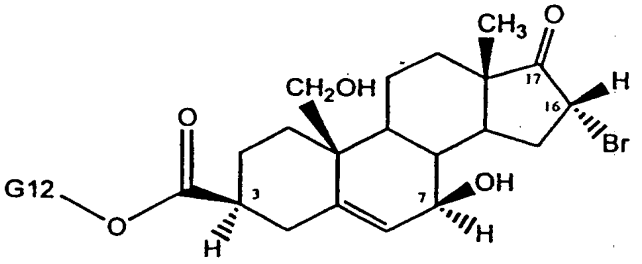
while the group 21-2 compound named 1.2.1.1 has the structure



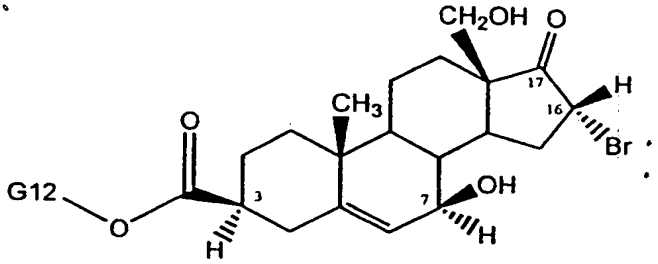
the group 21-3 compound named 1.2.1.1 has the structure



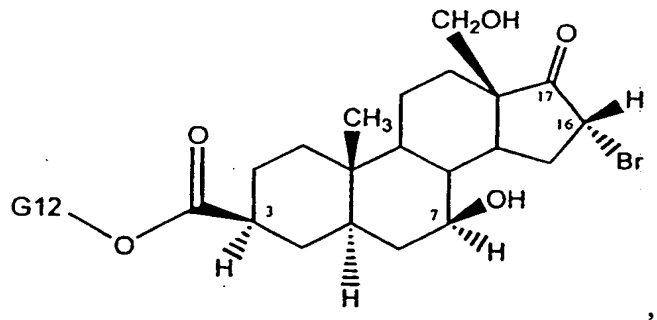
the group 21-4 compound named 1.2.1.1 has the structure



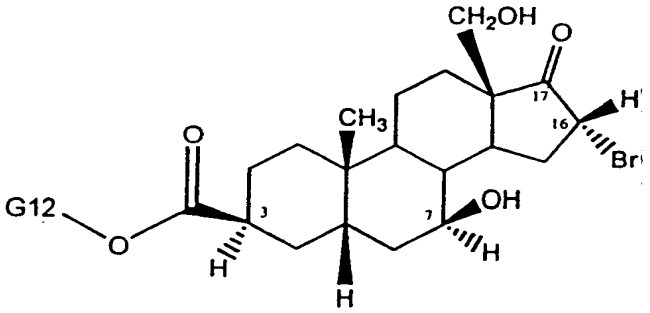
the group 21-6-1 compound named 1.2.1.1 has the structure



the group 21-6-2 compound named 1.2.1.1 has the structure



and the group 21-6-3 compound named 1.2.1.1 has the structure



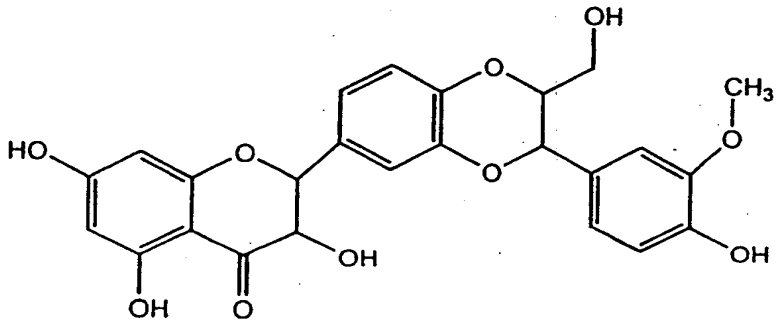
G12 in Group 21 is an organic moiety comprising 1, 2, 3, 4, 5, 6, 7, 8, 9 10, 11 or 12 carbon atoms and 0, 1, 2, 3, 4, 5, 6, 7 or 8 independently selected O, S, N, P, or Si atoms, but, if a Si or P atom is present, only one Si or P is present, wherein the organic moiety is optionally selected from C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, aryl, a C_{2-9} heterocycle or a substituted derivative of any of these comprising 1, 2, 3, 4 or more substituents, wherein each substituent is independently chosen and is selected from -O-, -S-, -NR^{PR}- (including -NH-), -C(O)-, =O, =S, -$N(R^{PR})_2$ (including -NH_2), -$C(O)OR^{PR}$ (including -C(O)OH), -$OC(O)R^{PR}$ (including -O-C(O)-H), -OR^{PR} (including -OH), -SR^{PR} (including -SH), -NO_2, -CN, -NHC(O)-, -C(O)NH-, -OC(O)-, -C(O)O-, -O-A8, -S-A8, -C(O)-A8, -OC(O)-A8, -C(O)O-A8, =N-, -N=, =N-OH, -$OPO_3(R^{PR})_2$, -OSO_3H_2 and halogen moieties or atoms, where each R^{PR} is -H, an independently selected protecting group or both R^{PR} together comprise a protecting group, and A8 is C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-4} alkyl-aryl (e.g., benzyl), aryl (e.g. phenyl) or C_{1-4} alkyl-C_{2-9} heterocycle. G12 moieties include -CH_3, -C_2H_5, -C_3H_7, -C_4H_9, -C_6H_{13}, -CH_2-C_6H_5, -C_2H_4-C_6H_5, -C_3H_6-C_6H_5, -C_6H_5, -CH_2-heterocycle, -CH_2-CH_2-heterocycle and a heterocycle, any of which are substituted with one, two, three or more independently selected -O-, -S-, -F, -Cl, -Br, -I, -NH-, =O, -CN, -OCH_3, -OC_2H_5, -OC_4H_9, -NO_2, -NH_2, -COOH, or -NH-C(O)- moieties.

Other embodiments include the use of any formula 4 compound or genus of formula 4 compounds that are named in any of the foregoing groups for any of the therapeutic or other applications described herein. This includes the use of any named formula 4 compound or genus for any of those applications wherein (i) R_2 is in the α-configuration, (ii) Q4 is -CH(halogen)-, (iii) X is in the α-configuration and the -H at the 17-position is in the β-configuration, (iv) Y is in the β-

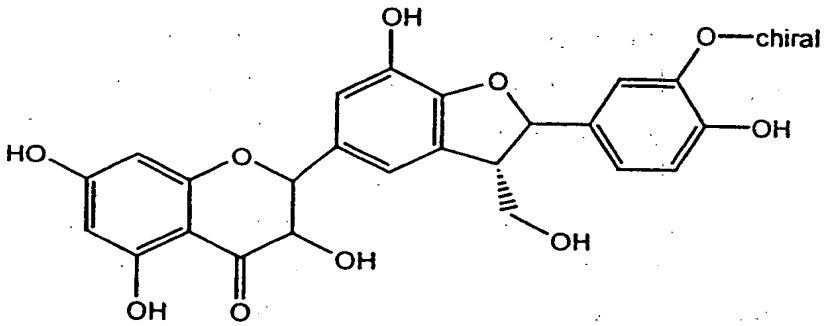
configuration and the -H at the 16-position is in the α-configuration or (v) R_1A is in the α-configuration and the -H at the 7-position is in the β-configuration.

Embodiments also include formula 1 compounds (e.g., formula 4 compounds) wherein R_4 is optionally substituted C_{1-8} alkyl, optionally substituted C_{2-8} alkenyl, optionally substituted C_{2-8} alkynyl, optionally substituted aryl, optionally substituted heterocycle, optionally substituted C_{1-8} alkyl-aryl, optionally substituted C_{1-8} alkyl-heterocycle or optionally substituted -CH_2-C_{1-8} organic moiety (where the organic moiety is as described for esters), wherein any of the foregoing are independently substituted with 1, 2, 3, 4, 5 or 6 or more -O-, -S-, -NH-, -NH-C(O)- (i.e., -NH-C(O)- or -C(O)-NH-), =O, =NOH, -NO_2, -CN, -F, -Cl, -Br, -I, -OH, -SH, or -NH_2. Such R_4 moieties include -CH_2-C_{1-6} optionally substituted alkyl, -CH_2-C_{2-6} optionally substituted alkenyl, -CH_2-C_{1-6} - optionally substituted aryl and -CH_2-C_{2-9} optionally substituted heterocycle.

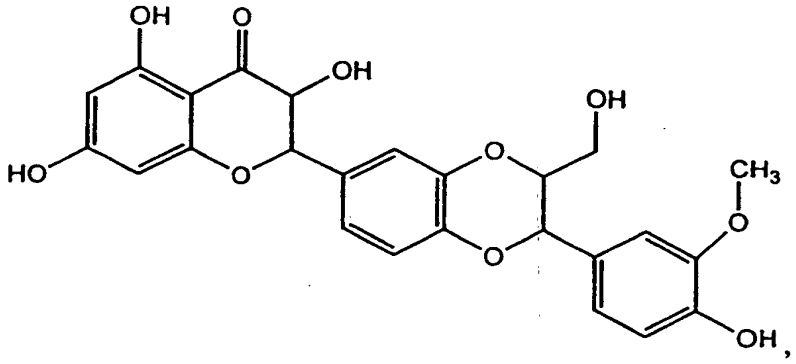
Plasma concentration-enhancing compounds. An aspect of the invention comprises administering an effective amount of a plasma concentration-enhancing compound, e.g., a compound of formula 2A or 2B compound with a formula 1 compound to facilitate preventing or treating one or more togavirus infections (including flavivirus, alphavirus, pestivirus or rubivirus) in a subject. In addition to the formula 2A and 2B compounds, the plasma concentration-enhancing compounds include bavachinin A, didymin (isosakuranetin-7-rutinoside or neoponcirin), flavanomarein (isookanine-7-glucoside), flavanone azine, flavanone diacetylhydrazone, flavanone hydrazone, silybin, which has the structure



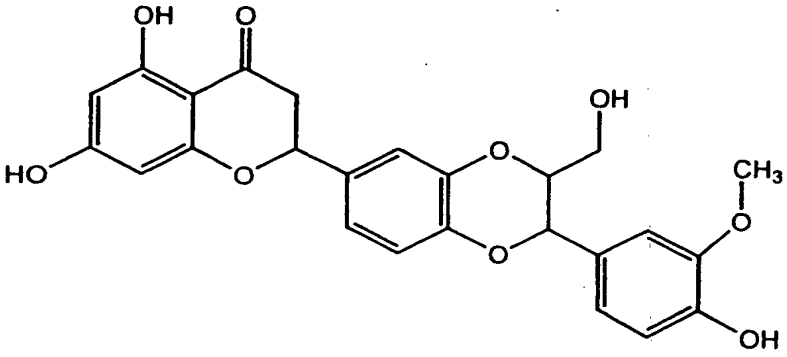
silychristin, which has the structure



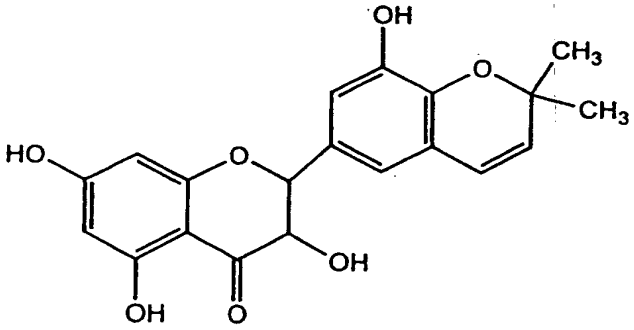
isosilybin, which has the structure



silandrin, which has the structure



and a compound having the structure (E)



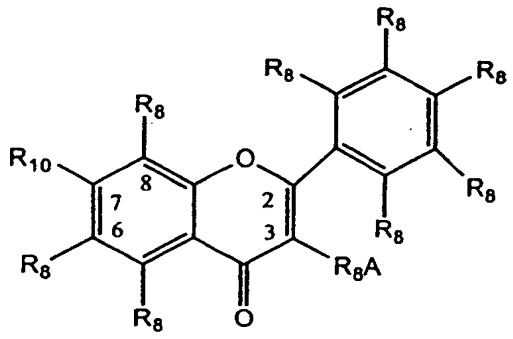
(E).

Collectively, these compounds and the formula 2A and 2B compounds are referred to as the "plasma concentration-enhancing compounds".

The formula 2A and 2B compounds encompass a number of natural and synthetic flavonoids, including certain flavones, flavans, and their iso analogs. The presence of a formula 2A or 2B compound in compositions comprising a formula 1 compound has been found to enhance the systemic bioavailability of formulations that comprise a formula 1 compound. The presence of a formula 2A or 2B compound, e.g., naringin or naringenin, results in enhanced plasma concentrations of the formula 1 compound. The formula 2A or 2B compound need not be present in a formulation that contains a formula 1 compound. The formula 2A or 2B compound can also be administered, e.g., about 1-4 hours, before or after, preferably before, the formula 1 compound is

administered. In these embodiments, one will administer an oral or parenteral formulation that contains a formula 1 compound and a formula 2A or 2B compound.

The plasma concentration-enhancing compounds include compounds of formulas 50-65



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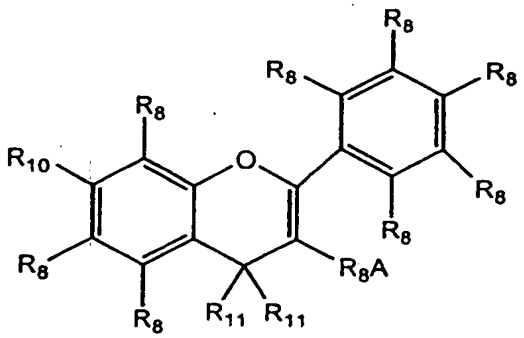

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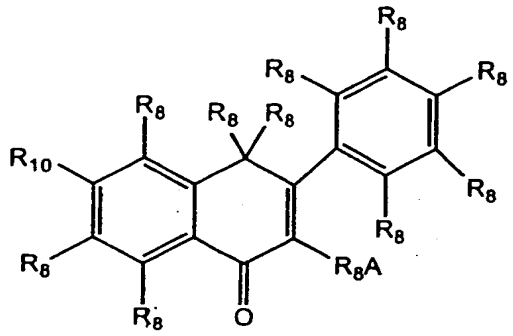

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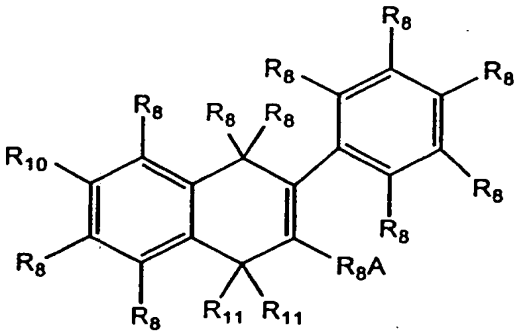

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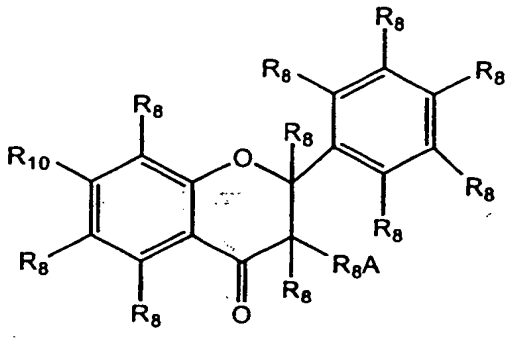

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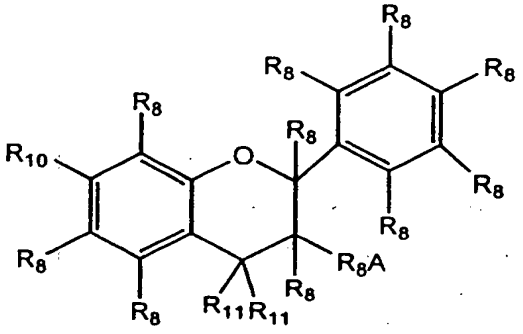

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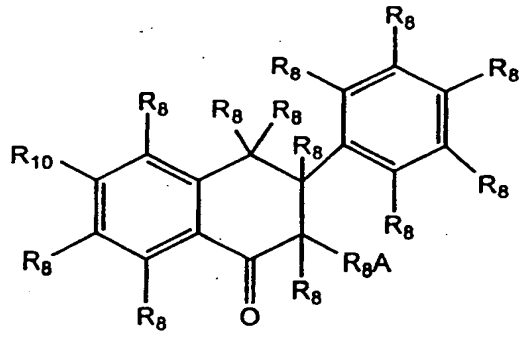

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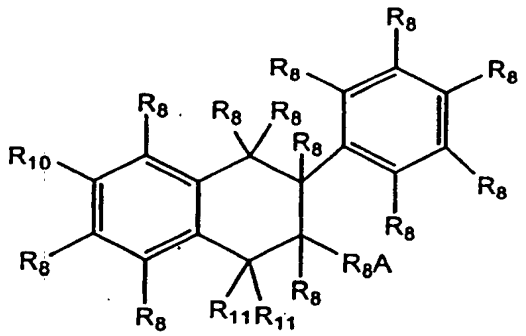

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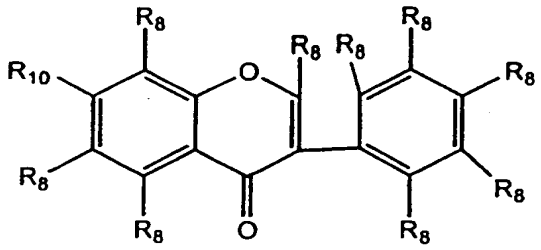

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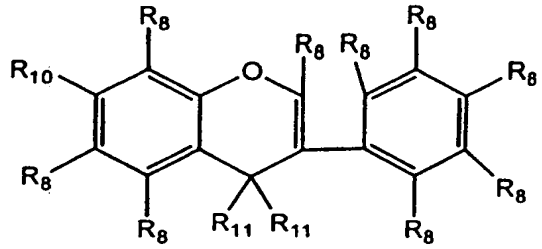

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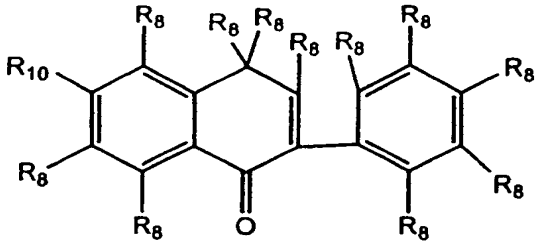

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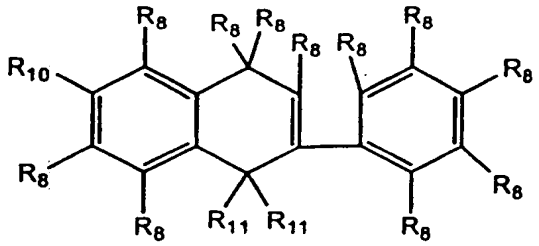

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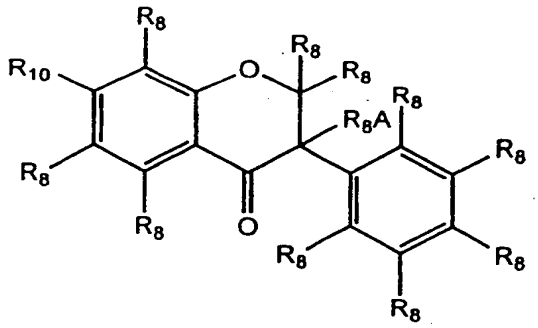

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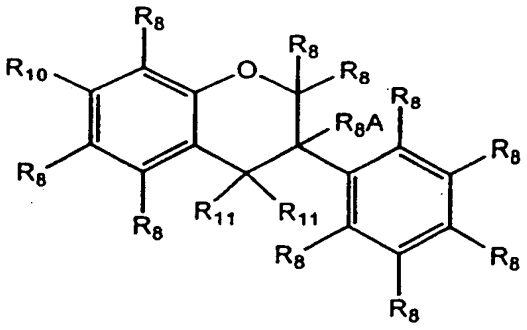

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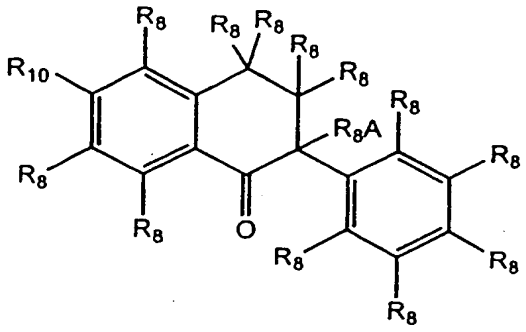

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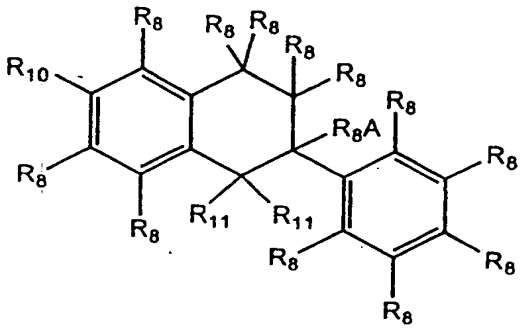


65

wherein

R_8 at the 6-position independently are -H, -OH, -F, -Cl, -Br, -I, C_{1-6} alkyl, C_{1-6} alkoxy, glucuronide, a C_{1-25} fatty acid, glucoside, $-CH_2CH=C(CH_3)_2$ or a group having the structure (B);

R_8 at the 8-position independently are -H, -OH, -F, -Cl, -Br, -I, C_{1-6} alkyl, C_{1-6} alkoxy, glucuronide, a C_{1-25} fatty acid, glucoside, $-CH_2CH=C(CH_3)_2$ or the residue of a formula 50-65 compound where a hydrogen atom is removed to form the formula 50-65 radical;

R_8A independently are -H, -OH, -F, -Cl, -Br, -I, C_{1-6} alkyl, C_{1-6} alkoxy, glucuronide, a C_{1-25} fatty acid, glucoside, $-CH_2CH=C(CH_3)_2$ or a group having the structure (C);

the remaining R_8 independently are -H, -OH, -F, -Cl, -Br, -I, C_{1-6} alkyl, C_{1-6} alkoxy, glucuronide, a C_{1-25} fatty acid or $-CH_2-CH=C(CH_3)_2$; and

R_{10} (i) is -OH or -F, -Cl, -Br, -I, C_{1-6} alkyl, C_{1-6} alkoxy, neohesperidoside, apioglucoside, rutinoside, glucoside, galactoside, rhamnoside, arabinoside, or a stereoisomer, hydrate, analog, derivative or metabolite of any of these moieties, any of which are optionally independently substituted at one or more hydrogen atoms with -OH, -F, -Cl, -Br, -I, C_{1-6} alkyl, C_{1-6} alkoxy, glucuronide or a C_{1-25} fatty acid, or (ii) R_{10} is the radical of bavachinin A, didymin, flavanomarein, flavanone azine, flavanone diacetylhydrazone, flavanone hydrazone, silybin, silychristin, isosilybin, silandrin, a moiety of structure (E) or a stereoisomer, hydrate, analog, derivative or metabolite of any of these moieties.

Additional therapeutic embodiments. In accordance with another preferred aspect of the present invention, there is provided a method of treatment of one or more of the conditions described above, e.g., togavirus infections, comprising administering a combination therapy including one or more of the compounds of the present invention administered simultaneously or sequentially with one or more macrophage stimulating factor (and optionally further co-administering one or more plasma concentration-enhancing compounds). Macrophage stimulating factors are well known to those of skill in the art, examples including GM-CSF (see, e.g., Callard et al., The Cytokine Facts Book, Academic Press, 1994, p. 139, which is incorporated herein by reference) and Interleukin-4 (sold by Immunex as "Leukine" and by Schering Plough as "Prokine").

In another preferred aspect of the present invention, the compounds of the present invention can be co-administered with one or more oxidation agent (optionally further together with a plasma

concentration-enhancing compound and/or a macrophage stimulating factor), or the patient may be given oxygen ventilation to increase oxidative steroids in the plasma.

In addition, the present invention is further directed to a combination therapy for the treatment of patients suffering from hepatitis C and/or hepatitis G, comprising administering to the patient, simultaneously or sequentially, one or more of the compounds of the present invention together with ribavirin and/or alpha interferon, and optionally further together with one or more plasma concentration-enhancing compound, one or more macrophage stimulating factor, one or more oxidation agent, and/or oxygen ventilation. In addition, the present invention is further directed to a combination therapy as discussed above in this paragraph for the treatment of patients suffering from or susceptible to any type of togavirus infection.

The invention also includes the use of combinations of compounds as disclosed herein in the manufacture of a medicament for use in the treatment of a togavirus or a flavivirus, in particular, HCV.

The components of any of the combination therapies disclosed herein can be administered simultaneously (in a combination formulation), essentially simultaneously (e.g., administration of each compound a few minutes or a few hours apart), or they can be administered sequentially, e.g., several days apart, or more than a week apart. For example, a compound of the present invention and a plasma-concentration-enhancing compound (and/or a macrophage stimulating factor) can be administered together, or essentially simultaneously, e.g., administration of each compound a few minutes or a few hours apart, or can be administered sequentially, e.g., several days apart, or more than a week apart (optionally together with simultaneous or sequential administration of oxidizing agent or oxygen ventilation). All such variations in administration of the combination therapy are encompassed within the scope of the invention.

The invention also includes pharmaceutical formulations containing any combination that is described herein.

The present invention is also directed to the use of compounds of the present invention in the manufacture of a medicament for therapeutic treatments as described herein, e.g., for treatment of a togavirus infection such as HCV.

The present invention is also directed to administering compounds of the present invention (optionally together with one or more combination compounds) to provide a prophylactic treatment of a patient to prevent, e.g., togavirus infections.

Articles of manufacture. The present invention also provides articles of manufacture comprising, for example, packaging material, at least one unit-dosage of a compound according to the present invention (optionally together with one or more unit-dosage of a compound which can be administered in a combination therapy) and a label or package insert indicating that the compound can be used in a method disclosed herein.

In one embodiment, an article of manufacture comprises packaging material, at least one unit dose of a 17-ketosteroid compound (a formula 1 compound) and a label or package insert indicating that the 17-ketosteroid compound (a formula 1 compound) can be used in a method as described herein. The packaging material can be made from one or more generally known materials, e.g., foam, cardboard, fiberboard, polystyrene and polypropylene, and is of a size suitable to contain the compound(s) accompanying the packaging material. A label or package insert can be a tag or label secured to the packaging material, a label printed on the packaging material or a label inserted within the packaging material. The label indicates that the 17-ketosteroid can be used in a therapy as disclosed herein, e.g., in combination with a plasma concentration-enhancing compound, a macrophage stimulating factor, ribavirin and/or alpha interferon. The label can also indicate that the compound(s) have received approval from an official agency, for example, the U.S. Food and Drug Administration, for medical or veterinary use according to the method. The label may also indicate suitable administration routes, dosage regimen, and the like. If desired, the article may contain additional components such as at least one unit dose of a plasma concentration-enhancing compound, macrophage stimulating factor, ribavirin and/or alpha interferon.

Methods of administration and formulations. The, dosage of a formula 1, 2A or 2B compound for a particular patient will vary depending on factors such as the overall health of the patient, the method, route and dose of administration and the severity of side effects (if any). Determination of the appropriate dose is made by the clinician using parameters known in the art. Generally, the -dose begins with an amount somewhat less than the optimum dose and it is increased by small increments thereafter until the desired or optimum effect is achieved. The dosage of the compounds of the invention is suitably determined depending on the individual cases taking symptoms, age and sex of the subject and the like into consideration. With respect to the duration of treatment, it is typical for skilled clinicians to monitor patients in order to determine when inhibition is providing therapeutic benefit, and to determine whether to increase dosage, decrease dosage, discontinue therapy, resume therapy or alter therapy.

The therapeutically effective dosage of any specific compound of the invention will vary somewhat from compound to compound and patient to patient. As a general proposition, a dosage in the range of from about 0.1 to about 500 mg/kg will have therapeutic efficacy. Typically, a dosage in the range of from about 0.5 mg/kg to about 500 mg/kg will be employed. A daily dosage of a formula 1 compound will typically comprise about 10 to about 750 mg, usually about 20 to about 400 mg, which may be administered as a single dose or as two or more subdoses. Such doses or subdoses may be administered at one or more sites or by one or more than one route of administration. The duration for the treatment is usually once per day for a sufficient length of time for the patient to become asymptomatic, or for symptoms to abate noticeably. Depending upon the severity of the infection in the individual patient, this may last several days, weeks, or longer.

With regard to the frequency and duration of treatment, it is well known that it is within the skill of the ordinary physician to monitor a patient's condition and to make appropriate decisions with regard to discontinuing, interrupting and resuming treatments.

The dosages used in accordance with the invention are suitably determined depending on the individual cases, taking symptoms, age and sex of the subject and the like into consideration. In addition, it is well known that it is within the skill of ordinary artisans to determine suitable dosages based on the above and other factors.

In accordance with the present method, a compound of the present invention may be administered orally, intramuscularly (IM); intravenously (IV), or subcutaneously (SC), with intravenous administration being especially preferred. Although other routes of administration can be used, it has been found that intravenous administration provides surprising effectiveness. For oral administration, the use of a plasma concentrationenhancing compound may be of great importance. Alternatively, a formula 1 compound or salt may also be administered intravenously or intramuscularly as a liposomal suspension. Such administration may comprise a cyclodextrin formulation (given orally, SC, IV or IM). Compounds of the invention and their pharmaceutically or physiologically, acceptable salts, are thus administered by any route suitable to the condition to be treated, including oral, rectal, nasal, topical (including ocular, buccal or sublingual), vaginal, parenteral (including subcutaneous, intramuscular, intravenous, intraperitoneal, intradermal, intrathecal, intradural and epidural) and pulmonary by aerosol. Generally, the compounds of the invention are administered parenterally, orally or topically. If an embodiment is not sufficiently orally bioavailable it can be administered by the other routes noted above.

Embodiments include formulations that comprise a liposome or lipid complex that comprises a formula 1 compound. Such formulations are prepared according to known methods, e.g., U.S. patents 4427649, 5043165, 5714163, 5744158, 5783211, 5795589, 5795987, 5798348, 5811118, 5820848, 5834016 and 5882678, all of which are incorporated herein by reference. The liposomes may optionally comprise an additional therapeutic or other agent(s), e.g., a compound of formula 2A or 2B. The liposomes can be delivered to a subject by any standard route, e.g., oral, aerosol or parenteral (e.g., SC, IV, IM).

Most often, the pharmaceutical compositions useful in the present invention will comprise a compound of formula 1, or a pharmaceutically acceptable salt thereof, in any pharmaceutically acceptable carrier. If a solution is desired, water is the carrier of choice with respect to water-soluble compounds or salts. In other embodiments, an organic vehicle, such as glycerol, ethanol, propylene glycol, polyethylene glycol, DMSO, $DMSO_2$, vegetable or mineral oils, ethanol, benzyl benzoate, or mixtures thereof, may be suitable. In general, the solutions in any instance should be sterilized in a suitable manner, preferably by filtration through a 0.22 micron filter. The compositions useful in the practice of the present invention may be provided in the form of vials, ampoules, and the like.

In some embodiments, the formula 1 compound that is present in the compositions or that is used in the methods disclosed herein is completely dissolved in non-aqueous excipients. However, in some embodiments, e.g., transient compositions or some formulations, the formula 1 compound is partially dissolved while the remaining portion is present as a solid, which can be a suspension or a colloid. In related embodiments, the formula 1 compound is incompletely dissolved and is present as a suspension or gel.

In addition to compounds of formula 1, or their salts, the pharmaceutical compositions may contain other additives, such as pH adjusting additives, in particular, agents such as acids, bases, or buffers, including sodium lactate, sodium acetate, and sodium gluconate. Further, such compositions may contain microbial preservatives, such as methylparaben, propylparaben, benzyl alcohol and benzyl benzoate. If a multiple use vial is supplied, the pharmaceutical composition should likewise include such a microbial preservative. The formulations may be lyophilized, using techniques well known in the art.

The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques, excipients and formulations generally are found in, e.g., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, PA 1985, 17th edition, Nema et al., *PDA J. Pharm. Sci. Tech.* 1997 51:166-171, both of which are incorporated herein by reference. Methods to make invention formulations include the step of bringing into association a formula 1 compound with one or more excipients or carriers. In general, the formulations are prepared by uniformly and intimately bringing into association the formula 1 compound with liquid excipients or finely divided solid excipients or both, and then, if appropriate, shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the formula 1 or formula 2A or 2B compound; as a powder or granules; as solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The formula 1 or formula 2A or 2B compound may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more excipients. Compressed tablets may be prepared by compressing in a suitable machine the formula 1 or formula 2A or 2B compound in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the formula 1 or formula 2A or 2B compound therein.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier, which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the emulsifying wax, and the wax together with the oil and fat make up the emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulgents and emulsion stabilizers suitable for use in formulations comprising a formula 1 or a formula 2A or 2B compound include Tween® 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

Formulations suitable for buccal administration include lozenges comprising a formula 1 or formula 2A or 2B compound in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the formula 1 or formula 2A or 2B compound in an inert basis such as gelatin and glycerin, or sucrose and acacia.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for intrapulmonary or nasal administration will have a particle size for example in the range of 0.01 to 200 microns (including particle sizes in a range between 0.01 and 500 microns in increments of 0.1 microns such as 0.1, 0.2, 0.3, 0.4, 0.5, 1, 2, 5, 30 microns, 35 microns, etc.), which is administered by inhalation through the nasal passage or by inhalation through the mouth so as to reach the various bronchi or alveolar sacs. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis of togavirus, flavivirus or retrovirus other infections. Inhalation therapy is readily administered by metered dose inhalers.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the formula 1 compound such carriers or excipients as are known in the art to be appropriate.

Formulations suitable for parenteral administration are sterile and include aqueous and non-aqueous injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials with elastomeric stoppers, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared

from sterile powders, granules and tablets of the kind previously described. Unit dosage formulations will typically contain a daily dose or unit daily sub-dose, as recited above, or an appropriate fraction thereof, of a formula 1 or formula 2A or 2B compound.

In some embodiments, the formula 1 compounds will be administered on an intermittent basis. In these embodiments, the formula 1 compound, e.g., a dose that comprises about 5-500 mg of a formula 1 compound (typically about 25-400 mg, or about 50-350 mg), is administered to a subject for at least one day, followed by no dosing for at least one day (at least 24 hours), optionally followed by at least one more daily dose of, e.g., about 50-500 mg. Intermittent dosing methods may comprise dosing (1, 2, 3 or 4 doses per week) based on a weekly schedule, e.g., dosing on Monday, Wednesday and Friday, or on Tuesday, Thursday Saturday for about 1, 2, 3, 4, 6, 8 or more weeks, followed by periods of about 2, 3, 4, 5, 30, 45, 60, 90 or more days with no dosing, optionally followed by dosing again on Monday, Wednesday and Friday for about 1, 2, 3, 4, 6, 8 or more weeks. Weekly dosing methods may comprise administration of the formula 1 compound to a subject 1, 2, 3, 4 or 5 times per week for 1, 2, 3, 4, or more weeks.. In related embodiments, dosing may be administered to a subject daily for 2, 3, 4, 5, 6, 7 or more days, followed by a period of about 1, 2, 3, 4, 5, 7, 14, 30, 45 60, 90 or more days, optionally followed by another course of daily dosing. These embodiments may further comprise treatment with a formula 2A or 2B compound or another treatment as described herein.

To the extent not already indicated, it will be understood by those of ordinary skill in the art that any one of the various specific embodiments herein described and illustrated may be further modified to incorporate features shown in any of the other embodiments disclosed herein.

Therapeutic applications. For therapeutic applications, the compositions disclosed herein will typically comprise one or more compounds of formula 1, and, the methods disclosed herein will utilize such compositions, which will contain one, two or more of such compounds, usually one. While it is possible for the compounds of the invention to be administered as pure compounds it is preferable to present them as pharmaceutical formulations. The formulations of the present invention comprise at least one formula 1 compound together with one or more acceptable carriers or excipients and optionally other therapeutic agents, e.g., a formula 2A or 2B compound(s), αIFN, ribavirin, a macrophage stimulating factor(s) and/or an oxidation agent(s). The one or more carriers or excipients must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the patient.

The compounds of this invention are useful in the treatment or prophylaxis of one or more flaviviral or togaviral infections in man or animals. Togavirus and flavivirus infections that can be treated with the formula 1 compounds include HCV, California encephalitis virus, St. Louis encephalitis virus, western equine encephalitis virus, eastern equine encephalitis virus, Colorado tick fever virus, LaCrosse encephalitis virus, Japanese encephalitis virus, yellow fever virus, Venezuelan equine encephalitis virus, Murray valley fever virus, tick-borne encephalitis viruses,

GB virus A, GB virus B, GB virus C, Dengue virus 1, Dengue virus 2, Dengue virus 3, Dengue virus 4, Semliki Forest virus and Sindbis virus. The rubiviruses include human rubella virus. Pestiviruses include mucosal disease viruses such as bovine virus diarrhea virus, hog cholera virus and sheep border disease virus. The formula 1 compounds are also useful to treat hepatitis G virus.

In addition to preventing or treating togaviral infections, the some of the formula 1 compounds can be used to treat subjects who are coinfected with a togavirus and another virus, such as a retrovirus or a second togavirus. Retroviruses such as a human immunodeficiency virus, e.g., HIV1 or HIV2, a simian immunodeficiency virus, a recombinant human-simian immunodeficiency virus (SHIV), a feline immunodeficiency virus or a feline or murine leukemia or sarcoma virus can be treated with formula 1 compounds. Coinfections with hepatitis viruses may be treated using the compounds of the invention, e.g., a HCV and HIV coinfection. In these embodiments, the subject will typically be one who has been tested to determine that (i) one or more togavirus infections is present (HCV, etc.) and (ii) a second virus infection is present (e.g., human herpes simplex virus 1, human herpes simplex virus 2, or a retrovirus such as HIV1, HIV2, etc.).

In other embodiments, a dosing regimen for a formula 1 compound will comprise the use of a relatively high induction dose, e.g., about 150-750 mg per day or about 150-750 mg per day using an intermittent dosing schedule (such as described herein), followed by lower maintenance dosing, e.g., about 50-250 mg per day or about 50-250 mg per day on an intermittent dosing schedule. These embodiments may further comprise treatment with a formula 2A or 2B compound or another treatment as described herein.

Parenteral formulations may comprise a cyclodextrin, e.g., an α-cyclodextrin, a β-cyclodextrin (e.g., β-hydroxypropylcyclodextrin) or a γ-cyclodextrin, which are typically employed in aqueous formulations, which optionally comprise one or more of a buffer, a salt (NaCl, etc.) to, e.g., render the solution isotonic, a bacteriostat or other excipients as known in the art and a formula 1 compound at a concentration of, e.g., about 5-25 mg/mL, typically about 10-20 mg/mL. Parenteral formulations that comprise a formula 1 compound and one or more excipients may be diluted into, e.g., sterile saline and infused into a subject. Parenteral formulations are typically administered by, e.g., intravenous, topical or oral delivery to a subject such as a human. For non-aqueous formulations, one or more solvents such as propylene glycol, a PEG, e.g., PEG 300 or PEG 400, ethanol, and benzyl benzoate may be employed. Typical aqueous and non-aqueous formulations will contain about 5 to about 400 mg/mL of a formula 1 compound, usually about 10 to about 200 mg/mL. Such parenteral formulations may be delivered orally, or by intramuscular, intravenous or subcutaneous injection.

In preparing compositions that comprise a formula 1 compound (and optionally one or more excipients), one may optionally mill or otherwise granulate the compound to obtain a desired particle size, before or after the formula 1 compound is contacted with one or more excipients. For

example, one may mill a formula 1 compound such as 16α-bromoepiandrosterone, to obtain an average particle size (or diameter) of about 0.5-25 μM or about 1-10 μM (e.g., about 2, 5 or 10 μM average particle size or diameter) before contacting the milled formula 1 compound with a liquid or solid excipient. Milled formula 1 compound is useful to facilitate dissolution or suspension of the formula 1 compound in one or more liquid excipients (e.g., a PEG such as PEG 300, propylene glycol or benzyl benzoate) or to facilitate uniformly distributing drug substance when the milled compound is contacted with one or more solid excipients (e.g., a filler, a binder or a lubricant).

The compositions and formulations disclosed herein are useful in the treatment of, or ameliorate one or more symptoms associated with, the conditions or infections disclosed herein. These compositions and formulations may also be used to treat, or ameliorate one or more symptoms associated with, a retroviral infection such as a HIV1 or HIV2 infection in humans, or Malaria in humans. As used herein, phrases such as "amelioration of one or more symptoms associated with" means that such compounds or formulations may be used to reduce replication of an infectious agent or to reduce the number of infectious agents that are present in a subject or to ameliorate one or more symptoms associated with, or caused by, the condition or infection (e.g., reduced fever, a shortened duration or degree of pain, or a noticeable reduction of or elimination of diarrhea or fatigue).

In addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring or coloring agents.

The present invention further provides veterinary compositions comprising at least one formula 1 or formula 2A or 2B compound together with a veterinary carrier therefor. Also, the formula 1 compound may be present in the animal's feed or water. Excipients for veterinary applications may include compounds, e.g., small amounts of chloroform, that may not be generally suitable for human use.

Veterinary carriers are materials useful for the purpose of administering the composition to cats, dogs, horses, mice, rats, hamsters, rabbits and other animals and may be solid, liquid or gaseous materials that are otherwise inert or acceptable in the veterinary art and are compatible with the formula 1 or formula 2A or 2B compound. These veterinary compositions may be administered orally, parenterally or by any other desired route, e.g., as described herein.

In an exemplary embodiment, human patients infected with HCV are given an aqueous isotonic α-cyclodextrin or β-cyclodextrin (e.g., β-hydroxypropyl cyclodextrin) formulation containing about 5-30 mg/mL of dehydroepiandrosterone or 16α-bromoepiandrosterone, e.g., about 10-20 mg/mL. The formulation is delivered intravenously in a single daily dose or two subdoses per day. The patients are dosed with 1 to 10 mg/kg/day for 4 to 10 days, followed by no dosing for 5 to 30 days, followed by dosing again with the cyclodextrin formulation for 4 to 10 days. The

dosing regimen is repeated one, two or more times. Clinical markers for HCV infection are followed during treatment, e.g., viral nucleic acid in the blood or plasma, liver enzyme levels in the blood or plasma (aminotransferase). For these patients, a standard anti-HCV treatment(s), e.g., interferon and/or ribavirin, is optionally started or continued according to the recommendations of the patient's doctor and with the patient's informed approval. In some of these embodiments, a formula 1 compound(s) is administered daily continuously as a component in an oral or parenteral composition or formulation, e.g., for a formula 1 compound(s) that is a new compound *per se*. The dehydroepiandrosterone or 16α-bromoepiandrosterone is optionally also administered systemically using, e.g., the formulation of example 1 to deliver 1-5 mg/kg/day every other day for about 1 to 4 months, or an oral formulation to deliver about 5-40 mg/kg/day every other day for about 1 to 4 months.

Embodiments of formula 1 compounds include or exclude any subset of compounds within the definition of formula 1, provided that at least one compound remains. For example, a subset of formula 1 compounds that are generally preferred and are usually included, for example are aqueous or nonaqueous formulations comprising 16α-bromoepiandrosterone. A subset compounds or applications for compounds that are optionally excluded from formula 1 compounds or their uses in any embodiment or claim herein comprises, e.g., the use of one or more compounds (or their use) that are disclosed in one or more prior art references or publications, to the extent that the disclosed compounds or uses renders any claim or embodiment unpatentable for novelty, obviousness and/or inventive step reasons. Another subset of the formula 1 compounds excludes one or more formula 1 compounds with corticosteroid activity, e.g., one or more formula 1 compounds wherein the 3-position comprises =O, a double bond at the 4-5 positions, a hydroxyl group (-OH) is bonded to the 11-position, -C(O)-CH_2OH and -H or -C(O)-CH_2OH and -OH or =O is bonded to the 17-position, Q_6 is -CH_3 or -CH_2OH, Q_3 is -CH_3, and the remaining positions (R_1) comprise, e.g., -H and 0, 1 or 2 hydroxyl groups.

In other embodiments, a formula 1 compound may be linked to an oligonucleotide or an oligonucleotide analog to facilitate delivery of the oligonucleotide or analog into cells. Typically the formula 1 compound will be linked to the steroid nucleus through a terminal hydroxyl group at a 5', 3' or 2' position of the oligonucleotide. Oligonucleotides and analogs of oligonucleotides are known and have been described, e.g., U.S. patents 4725677, 4973679, 4997927, 4415732, 4458066, 5047524, 4959463, 5212295, 5386023, 5489677, 5594121, 5614622, 5624621; and PCT publication Nos. WO 92/07864, WO 96/29337, WO 97/14706, WO 97/14709, WO 97/31009 and WO 98/04585, WO 98/04575 all of which are incorporated herein by reference.

Synthesis methods. The compounds employed in the present invention in general may be synthesized in manners known and readily understood by those skilled in the art. Therefore, there is no need to explain in great detail the methodology used for the synthesis of most such compounds.

Formula 1 compounds that comprise a thioacetal moiety, sulfate ester, sulfite ester, carbamate or thioester moiety at R_2 (the 3-position) are prepared essentially according to methods known in the art. Suitably protected intermediates will be used as is apparent. See, for example, U.S. patent 5198432; European patent publications EP 576915 and EP 576914; C. Christiana et al., *J. Chem. Soc. Chem. Commun.* 1991 vol 22, C. Christiana et al., *J. Chem. Soc. Chem. Commun.* 1991 19:1403-1405, H.N. Abramson et al., *J. Pharm. Sci.* 1977 66:602-603, E.J. Corey et al., *J. Am. Chem. Soc.* 1996 118:8765-8766, A.G.M. Barrett et al., *J. Org. Chem.* 1989 54:227, D.H.R. Barton et al., *J. Chem. Soc. Perkin Trans. 1* 1976 19:2112-2116, D.H.R. Barton et al., *J. Chem. Soc. Perkin Trans. 1* 1975 16:1574-1585 and W.T. Smith et al., *Trans. Kentucky Acad. Sci.* 1984 45:76-77, all of which are incorporated herein by reference.

Enumerated embodiments. Aspects of the invention include the following enumerated embodiments, which further illustrate the invention and preferred aspects thereof or related subject matter.

1. A method of treating hepatitis virus C in a patient in need of such treatment, comprising administering to said patient an effective amount of at least one compound selected from the group consisting of the compounds of the present invention.

2. A method as recited in embodiment 1, further comprising administering to said patient at least one plasma concentration-enhancing compound.

3. A method as recited in embodiment 2, wherein said at least one compound according to the present invention and said at least one plasma concentration-enhancing compound are administered simultaneously.

4. A method as recited in embodiment 2, wherein said at least one compound according to the present invention and said at least one plasma concentration-enhancing compound are administered sequentially.

5. A method as recited in any one of embodiments 1 - 4, further comprising administering to said patient ribavirin and/or alpha interferon.

6. A method as recited in any one of embodiments 1 - 5, further comprising administering to said patient at least one macrophage stimulating factor.

7. A method as recited in any one of embodiments 1 - 6, further comprising administering to said patient one or more oxidation agent and/or oxygen ventilation.

8. A method as recited in any one of embodiments 1 - 7, wherein said patient is a mammal.

9. A method as recited in embodiment 8, wherein said patient is a human.

10. A method as recited in any one of embodiments 1 - 9, wherein said administering is by injection.

11. A method as recited in any one of embodiments 1 - 9, wherein said administering is by infusion.

12. A method as recited in any one of embodiments 1 - 9, wherein said administering is by intravenous injection.

13. A method as recited in embodiment 2, wherein said plasma concentration-enhancing compound is naringin or naringenin.

14. A method of reducing at least one aminotransferase level in a patient suffering from hepatitis virus C in a patient in need of such treatment, comprising administering to said patient an effective amount of at least one compound selected from the group consisting of the compounds of the present invention.

15. A method as recited in embodiment 14, further comprising administering to said patient at least one plasma concentration-enhancing compound.

16. A method as recited in embodiment 14, wherein said at least one compound according to the present invention and said at least one plasma concentration-enhancing compound are administered simultaneously.

17. A method as recited in embodiment 15, wherein said at least one compound according to the present invention and said at least one plasma concentration-enhancing compound are administered sequentially.

18. A method as recited in any one of embodiments 14 - 17, further comprising administering to said patient ribavirin and/or alpha interferon.

19. A method as recited in any one of embodiments 14 - 18, further comprising administering to said patient at least one macrophage stimulating factor.

20. A method as recited in any one of embodiments 14 - 19, further comprising administering to said patient one or more oxidation agent and/or oxygen ventilation.

21. A method as recited in any one of embodiments 14 - 20, wherein said patient is a mammal.

22 A method as recited in embodiment 21, wherein said patient is a human.

23. A method as recited in any one of embodiments 14 - 22, wherein said administering is by injection.

24. A method as recited in any one of embodiments 14 - 22, wherein said administering is by infusion.

25. A method as recited in any one of embodiments 14 - 22, wherein said administering is by intravenous injection.

26. A method as recited in embodiment 15, wherein said plasma concentration-enhancing compound is naringin or naringenin.

27. A method of treating a togavirus in a patient in need of such treatment, comprising administering to said patient an effective amount of at least one compound selected from the group consisting of the compounds of to the present invention.

28. A method as recited in embodiment 27, further comprising administering to said patient at least one plasma concentration-enhancing compound.

29. A method as recited in embodiment 28, wherein said at least one compound according to the present invention and said at least one plasma concentration-enhancing compound are administered simultaneously.

30. A method as recited in embodiment 28, wherein said at least one compound according to the present invention and said at least one plasma concentration-enhancing compound are administered sequentially.

31. A method as recited in any one of embodiments 27 - 30, further comprising administering to said patient ribavirin and/or alpha interferon.

32. A method as recited in any one of embodiments 27 - 31, further comprising administering to said patient at least one macrophage stimulating factor.

33. A method as recited in any one of embodiments 27 - 32, further comprising administering to said patient one or more oxidation agent and/or oxygen ventilation.

34. A method as recited in any one of embodiments 27 - 33, wherein said patient is a mammal.

35. A method as recited in embodiment 34, wherein said patient is a human.

36. A method as recited in any one of embodiments 27 - 35, wherein said administering is by injection.

37. A method as recited in any one of embodiments 21 - 35, wherein said administering is by infusion.

38. A method as recited in any one of embodiments 27 - 35, wherein said administering is by intravenous injection.

39. A method as recited in embodiment 28, wherein said plasma concentration-enhancing compound is naringin or naringenin.

40. A method according to embodiment 27, wherein said togavirus is an alphavirus.

41. A method according to embodiment 27, wherein said togavirus is a flavivirus.

42. A method according to embodiment 41, wherein said flavivirus is hepatitis G.

43. A method according to embodiment 41, wherein said flavivirus is yellow fever virus.

44. A method according to embodiment 27, wherein said togavirus is a rubivirus.

45. A method according to embodiment 44, wherein said rubivirus is the rubella virus.

46. A method according to embodiment 27, wherein said togavirus is a pestivirus.

47. A method according to embodiment 46, wherein said pestivirus is bovine virus diarrhea virus (BVDV).

48. The method of any of embodiments 1-47 wherein the compound of the invention is a formula 1 compound or a metabolite thereof.

49. The method of embodiment 48 wherein the formula 1 compound is a compound named in compound groups 1-21, or in any formula 1 (e.g., any formula 4) compound or genus disclosed or named herein, or a metabolite of any of these.

50. A composition comprising 16α-bromoepiandrosterone, and 2, 3, 4 or 5 excipients selected from polyethylene glycol, dehydrated ethanol, benzyl benzoate, benzyl alcohol and propylene glycol, wherein the composition comprises less than about 3% v/v, or less than about 1% v/v, or less than about 0.5% v/v of water, or less than about 0.1% v/v of water.

51. The composition of embodiment 50 wherein the composition comprises (i) 16α-bromoepiandrosterone at a concentration of about 45-55 mg/mL, (ii) 20-30% v/v polyethylene glycol 300, polyethylene glycol 400 or a mixture of polyethylene glycol 300 and 400, (iii) 10-15% v/v dehydrated ethyl alcohol, 2.5-7.5% v/v benzyl benzoate, and (iv) 55-60% v/v propylene glycol.

52. The composition of embodiment 51 wherein the composition comprises 16α-bromoepiandrosterone at a concentration of about 50 mg/mL, about 25% v/v polyethylene glycol 300, about 12.5% v/v dehydrated ethyl alcohol, about 5% v/v benzyl benzoate, about 57.5% v/v propylene glycol and less than about 0.5% v/v water.

53. The composition of embodiment 50 wherein the composition comprises 16α-bromoepiandrosterone at a concentration of about 50-105 mg/mL, about 27-33% w/w benzyl benzoate, about 27-33% w/w polyethylene glycol 300, about 25-30% w/w propylene glycol and about 1-3% w/w benzyl alcohol.

54. The composition of embodiment 53 wherein the composition comprises 16α-bromoepiandrosterone at a concentration of about 100 mg/mL (about 10% w/w), about 30.4% w/w benzyl benzoate, about 30.7% w/w polyethylene glycol 300, about 28% w/w propylene glycol and benzyl alcohol about 1.9% w/w.

55. A product produced by the process of contacting 16α-bromoepiandrosterone and a liquid excipient, wherein the product contains less than about 3% water, provided that the liquid excipient is not chloroform, dimethylsulfoxide, olive oil, or a vegetable oil.

56. The product of embodiment 55 wherein the liquid excipient is polyethylene glycol, dehydrated ethanol, benzyl benzoate, benzyl alcohol and propylene glycol, wherein the product comprises less than about 3% v/v, or less than about 1% v/v, or less than about 0.5% v/v of water.

57. The use of a formula 1 compound for making a medicament for the treatment of an infection caused by one or more togaviruses in a subject.

58. The use of embodiment 57 wherein the formula 1 compound is a compound named in compound groups 1-21, or a metabolite thereof.

59. A method to enhance the oral bioavailability of a therapeutic agent comprising administering to a subject an effective amount of a compound of formula 2A or 2B.

60. The method of embodiment 59 wherein the therapeutic agent is a steroid, a steroid analog an antibiotic, an antiviral agent (e.g., a nucleoside, nucleoside analog, nucleotide analog, protease inhibitor or a polymerase inhibitor) or an antifungal agent (e.g., amphotericin B).

61. The method of embodiment 59 wherein the therapeutic agent is a compound of formula 1.

62. A method comprising administering an effective amount of a composition of any of embodiments 50-54 to a subject having, or susceptible to, a togavirus infection (e.g., HCV).

63. The method of embodiment 62 wherein the subject is a human and the human is optionally coinfected with a retrovirus (e.g., HIV1 or HIV2).

64. A method to ameliorate or reduce one or more symptoms associated with a togavirus infection in a subject, or to reduce replication of a togavirus in a subject infected with a togavirus, comprising administering to the subject an effective amount of a compound of formula 1.

65. The method of embodiment 64 wherein the formula 1 compound is a compound or within a genus of compounds as disclosed herein, e.g., a compound or genus named in compound groups **1-21** or in the claims as originally filed, or the formula 1 compound is present in a composition comprising one or more pharmaceutical excipients, e.g., any of the formulations disclosed or described herein.

66. A composition comprising a formula 1 compound wherein the formula 1 compound is a compound or within a genus of compounds as disclosed herein, e.g., a compound or genus named in compound groups **1-21** or in the claims as originally filed, and at least one excipient and a local anesthetic, wherein the local anaesthetic is optionally selected from procaine, benzocaine and lidocaine.

67. A product produced by the process of contacting a compound of formula 1, e.g., any compound named in compound groups **1-21**, and a first excipient with a second excipient wherein the product optionally further comprises a local anesthetic, wherein the local anaesthetic is optionally selected from procaine, benzocaine and lidocaine.

68. A product produced by the process of contacting a compound of formula 1, e.g., any compound named in compound groups **1-21**, and a first nonaqueous liquid excipient with a second nonaqueous liquid excipient wherein the product comprises less than about 3% w/w water, or less than about 0.5% w/w water, or less than about 0.1% w/w water, and wherein the first or the second nonaqueous liquid excipient optionally excludes one or more of dimethylsulfoxide, chloroform, dioxane, a vegetable oil and olive oil, and wherein the product optionally further comprises a local anesthetic, wherein the local anaesthetic is optionally selected from procaine, benzocaine and lidocaine.

69. A method comprising administering an effective amount of the composition of embodiment 66 or the product of embodiments 67 or 68 to a subject having an infection or

condition described herein, e.g., HCV, whereby the infection or condition, or a symptom thereof, is eliminated, reduced, treated, improved or ameliorated.

70. The method of embodiment 69 wherein the formula 1 compound is 16α-haloepiandrosterone or 16α-halodehydroepiandrosterone.

EXAMPLES

The following examples further illustrate the invention and are not to be construed as limiting the invention.

Example 1. 16α-Bromoepiandrosterone formulation 1. Two lots of a non-aqueous formulation was made at a 16α-bromoepiandrosterone ("BrEA") concentration of 50 mg/mL in 25% polyethylene glycol 300, 12.5% dehydrated ethyl alcohol, 5% benzyl benzoate, and 57.5% propylene glycol, hereafter "formulation 1", as follows. BrEA was obtained from Procyte, Inc. The remaining excipients are shown below.

Excipient	Specification	Supplier Lot No.	Final Product Concentration
Propylene glycol	USP	Arco Chemical HOC-61220-01104	57.5% (v:v)
Polyethylene glycol 300	NF	Union Carbide 695752	25% (v:v)
Dehydrated alcohol (ethanol)	USP	McCormick Distilling 97K10	12.5% (v:v)
Benzyl benzoate	USP	Spectrum Pharmaceuticals MG025	5% (v:v)

The formulation was prepared by suspending BrEA in polyethylene glycol 300, and sequentially adding propylene glycol, benzyl benzoate, and dehydrated ethyl alcohol to form a solution, which was diluted to the final desired volume with additional propylene glycol. The procedure is described below.

The calculated amount of polyethylene glycol 300 was added to a compounding vessel. Then, while mixing, the calculated amount of BrEA was added to the vessel, and mixed for at least 5 minutes to form a smooth, creamy liquid. Propylene glycol was added to the vessel, and mixed for a minimum of 5 minutes to form a uniform suspension. The calculated amount of benzyl benzoate is added to the vessel, and mixed for approximately 5 minutes to form a translucent liquid suspension. Dehydrated alcohol was added to the vessel, and mixed for approximately 5 minutes to form a clear, colorless solution. Propylene glycol was then added to achieve the desired final formulation, and mixed for approximately 5 minutes. The drug solution was transferred to a volume-dispensing device set to deliver 1.2 mL per vial. Under nitrogen pressure, the solution was

filtered through two 0.2 μm polyvinylidene fluoride filters in series before dispensing into 2 cc amber galss vials. The vials were capped with Teflon-coated, butyl-rubber stoppers and crimp sealed.

Materials used in the product vials are listed below.

Material	Source	Product Code	Description
Vial	Wheaton	2702-B51BA	Tubing vial, 2 mL/13 mm, glass, type 1 amber
Stopper	Omniflex	V9239 FM257/2	13 mm, Teflon coated, butyl rubber stopper
Seal	West	4107	Flip seal, 13 mm, mist gray bridge

Example 2. BrEA formulation 2. A formulation containing 100 mg/mL of BrEA, 10% w/w, in benzyl benzoate (USP) 30.4% w/w, polyethylene glycol 300 (NF) 30.7% w/w, propylene glycol (USP), qs, about 28% w/w and benzyl alcohol (NF) 1.9% w/w, hereafter "formulation 2", was prepared as follows. A desired amount of BrEA (1.0 kg) was suspended in PEG 300 (about 3.0 L) in a compounding vessel and mixed for at least 5 minutes at room temperature to form a smooth creamy liquid. The needed amount of propylene glycol (about 1.5 L) was then added and mixing was continued for at least 5 minutes to form a uniform suspension. Benzyl benzoate (about 3.0 L) was then added and the vessel contents were mixed for about 5minutes to form a translucent suspension. Benzyl alcohol (about 200 mL) was then added and the mixing was continued for about 5 minutes to form a clear, colorless solution. Propylene glycol was then added to achieve the desired final formulation volume (about 1.5 L) and mixing was continued for about 5 minutes. The drug solution was transferred to a volume-dispensing device, which was set to deliver 1.2 mL per vial (2 mL, glass, type 1 amber vials). The formulation was filtered under nitrogen pressure (about 3 atm) through two 0.2 μm polyvinylidine fluoride filters in series. The vials were capped using Teflon-coated, butyl rubber stoppers and then crimp sealed essentially as described in example 1. The vials were stored in the dark at reduced temperature (about 2-8°C).

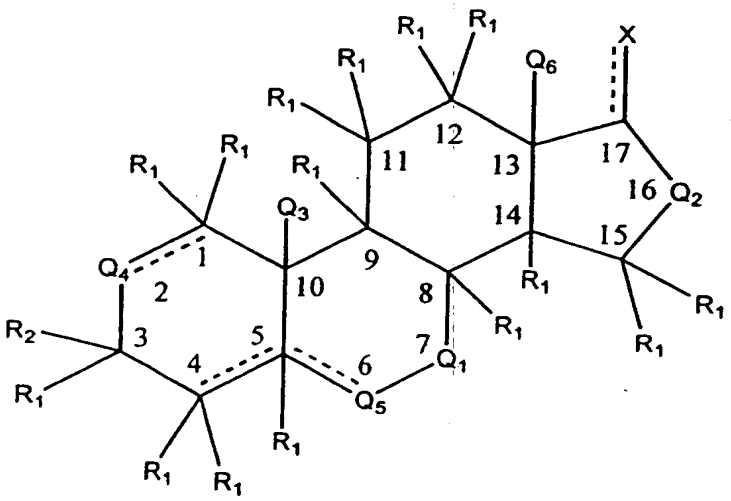
Example 3. Human clinical trial. A clinical trial protocol that incorporates about 15-20 patients is designed. For the phase I or I/II trial, the patients are mildly infected with one or more togaviruses, e.g., HCV and they are mildly to moderately symptomatic. The patients are administered treatment for 1, 2 or 3 weeks. In 2 or more dose groups, e.g., 25, 50 or 100 mg/day of 16α-bromoepiandrosterone (BrEA), or an ester thereof, is administered parenterally, e.g., by intramuscular or intravenous injection, on 3, 4 or 5 days of the weeks when dosing occurs. Dosing is on consecutive days or on an intermittent schedule, e.g., 2, 3 or 4 doses with one dose administered every other day. The formulation containing BrEA is as described herein, e.g., the formulation of example 1 or 2, preferably the formulation of example 2. During the week of treatment and for 1, 2, 3, or more weeks thereafter, blood samples are taken periodically for evaluation of the infection or its symptoms, pharmacokinetics, plasma cytokines (e.g., IL-2, IL-4,

IL-10, IGF1, γIFN, GM-CSF), and intracellular cytokines (e.g., IL-2, IL-4, IL-10, IGF1, γIFN, GM-CSF). The patients are optionally treated again at about 2 to 12 weeks after the initial dosing, using the same or a similar protocol as that used in the initial dosing protocol.

CLAIMS

What is claimed is:

1. A method to treat or prevent togaviral infection, or to ameliorate or reduce one or more symptoms of a togaviral infection, in a subject suffering from or susceptible to the togaviral infection, comprising administering to the subject an effective amount of a compound having formula 1,



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wherein

Q_1 is $-C(R_1)_2-$ or -C(O)-;

Q_2 is $-C(R_1)_2-$, $-C(R_1)(Y)-$, -C(Y)- or $-CH_2-CH_2-$;

Q_3 is -H or $-C(R_1)_3-$;

Q_4 is $-C(R_1)_2-$, -C(O)-, hydroxyvinylidine or methyl methylene;

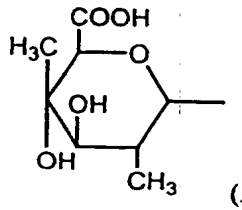
Q_5 is $-C(R_1)_2-$ or -C(O)-;

X and Y independently are -OH, -H, lower alkyl, -O-C(O)-R_5, -C(O)-OR_5, halogen or =O;

each R_1 independently is -H, halogen, -OH, C_{1-6} alkoxy, or C_{1-6} alkyl;

R_2 is -H, -OH, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, $-OR_3$, an ester, a thioester, a thioacetal, a sulfate ester, a sulfonate ester or a carbamate or R_2, together with the R_1 that is bonded to the same carbon atom is =O;

R_3 is -S(O)(O)-OM, $-S(O)(O)-O-CH_2-CH(O-C(O)-R_6)-CH_2-O-C(O)-R_6$, $-P(O)(O)-O-CH_2-CH(O-C(O)-R_7)-CH_2-O-C(O)-R_7$, a glucuronide group of structure (A)



(A),

or R_3 is C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, a C_{1-18} ester or a C_{1-18} thioester, where any of the foregoing C_{1-18} or C_{2-18} moieties are optionally substituted at one or more hydrogen atoms with one or more independently selected $-OR^{PR}$, $-NHR^{PR}$, or $-SR^{PR}$, groups, or R_3 is a C_{1-18} fatty acid, C_{2-10} alkynyl, $(J)_n$-phenyl-C_{1-5}-alkyl, $(J)_n$-phenyl-C_{2-5}-alkenyl;

each R_5 independently is straight or branched C_{1-14} alkyl;

each R_6 independently is C_{1-14} straight or branched alkyl; and

each R_7 independently is C_{1-14} straight or branched alkyl or a glucuronide group of structure (A);

each R^{PR} independently is -H or an independently selected protecting group;

n is 0, 1, 2 or 3;

each J independently is halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, carboxy, nitro, sulfate, sulfonyl, a C_{1-6} carboxyl ester or a C_{1-6} sulfate ester;

M is hydrogen, sodium, $-S(O)(O)-O-CH_2-CH(O-C(O)-R_6)-CH_2-O-C(O)-R_6$, $-P(O)(O)-O-CH_2-CH(O-C(O)-R_7)-CH_2-O-C(O)-R_7$ or a glucuronide group of structure (A); and

the dotted lines represent an optional double bond, provided that there are not double bonds at both the 4-5 and 5-6 positions and provided that when a double bond is present, zero or 1 R_1 group is bonded to carbon atoms at the 1-, 2-, 4-, 5-, 6- or 17 positions so that these carbon atoms are tetravalent; and

the salts, stereoisomers, positional isomers, metabolites, analogs, precursors, hydrates, tautomers, ionized forms and solvates thereof.

2. The method of claim 1 wherein the togaviral infection is one or more of a flavivirus infection, a pestivirus infection, a rubivirus infection or an alphavirus infection.

3. The method of claim 2 wherein the formula 1 compound is one or more compounds selected from compound groups **1-21**.

4. The method of claim 2 wherein the togaviral infection is an infection caused by one or more of hepatitis C virus, a hepatitis G virus, California encephalitis virus, St. Louis encephalitis virus, Western equine encephalitis virus, Eastern equine encephalitis virus, Colorado tick fever virus, LaCrosse encephalitis virus, Japanese encephalitis virus, yellow fever virus, Venezuelan equine encephalitis virus, Murray valley fever virus, GB virus A, GB virus B, GB virus C, Dengue virus 1, Dengue virus 2, Dengue virus 3, Dengue virus 4, Semliki Forest virus, human rubella virus and bovine viral diarrhea virus.

5. The method of claim 4 wherein the formula 1 compound is one or more compounds selected from compound groups **1-21**.

6. The method of claim 4 wherein the togaviral infection is an infection caused by HCV, HGV, yellow fever virus, rubella virus or bovine virus diarrhea virus.

7. The method of claim 5 wherein the subject is a human or a primate.

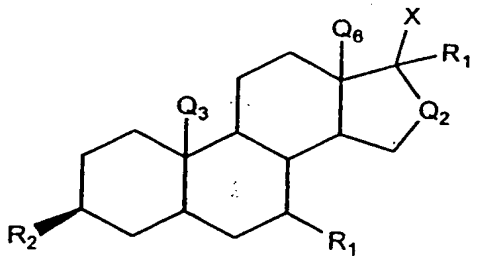
8. The method of claim 7 wherein the formula 1 compound is one or more compounds selected from compound groups **1-21**.

9. The method of claim 8 wherein the formula 1 compound is 16α-bromo-3β-hydroxy-5α-androstan-17-one or 16α-bromodehydroepiandrosterone.

10. The method of claim 1 wherein the subject is coinfected with a retrovirus.

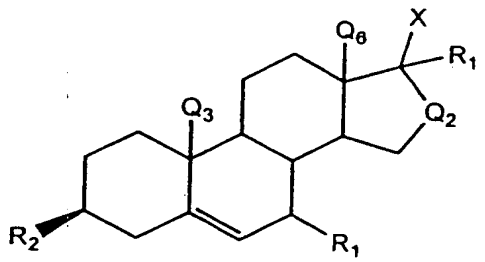
11. The method of claim 10 wherein the subject is a human and the retrovirus is HIV1 or HIV2.

12. The method of claim 1 wherein the formula 1 compound has the formula 1B or 1C



1B

or



1C

wherein,

each R_1 independently is -H, -OH, a halogen, -CHCH$_2$, -CHCHCH$_3$, -CCH, -CCCH$_3$, or, R_1, together with the hydrogen atom that is bonded to the same carbon atom comprises =O;

R_2 is -O-C(O)-R_4, -S-C(O)-R_4, -O-S(O)(O)-R_4, -O-S(O)(O)-OR_4, -O-C(O)-NHR_4, or -O-C(S)-R_4;

R_4 is -H, a protecting group, optionally substituted C_{1-18} alkyl, optionally substituted C_{1-18} alkenyl, optionally substituted C_{1-18} alkynyl, optionally substituted aryl, optionally substituted aryl-C_{1-6} alkyl, optionally substituted aryl-C_{2-6} alkenyl, optionally substituted aryl-C_{2-6} alkynyl, optionally substituted heterocycle-C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl-heterocycle, optionally substituted C_{2-6} alkynyl-heterocycle or an optionally substituted heterocycle, where any of the foregoing moieties are optionally substituted at one or more carbon or hydrogen atoms with one or more independently selected -O-, -S-, -NR^{PR}-, -OR^{PR}, -NHR^{PR}, -SR^{PR}, =O, =S, =N-OH, -CN, -NO$_2$, -F, -Cl, -Br or -I groups or atoms;

each R^{PR} independently is -H or an independently selected protecting group;

Q_2 is -C(R_1)$_2$-; and

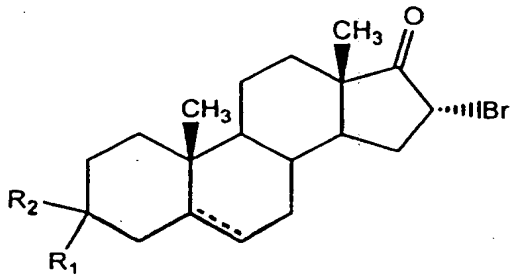
Q_3 and Q_6 independently are -H, -CH$_3$ or -CH$_2$OH.

13. The method of claim 12 wherein Q_3 and Q_6 are both -CH$_3$ in the β-configuration; and

Q_2 is -CH$_2$-, -C(O)-, -CH(Br)-, -CH(I)-, or -CH(OH)- with the Br, I or OH moieties in the α-configuration, or Q_2 comprises -C(O)- or -CH$_2$-CH$_2$-; and

R_1 at the 7-position is -H, -OH or, when taken with the hydrogen atom that is bonded to the same carbon atom, R_1 is =O.

14. The method of claim 1 wherein the formula 1 compound has the formula 1A



1A

wherein,

R_2 is -OH, halogen, C_{1-6} alkoxy, $-OR_3$, a C_{1-18} fatty acid, C_{1-10} alkynyl, $(J)_n$-phenyl-C_{1-5}-alkyl, $(J)_n$-phenyl-C_{1-5}-alkenyl, an ester optionally selected from -O-C(O)-$(CH_2)_m$-R_4 and -C(O)-O-$(CH_2)_m$-R_4, or R_2 is -S-C(O)-$(CH_2)_m$-R_4, -C(O)-S-$(CH_2)_m$-R_4, -O-S(O)(O)-$(CH_2)_m$-R_4, -O-S(O)(O)-O-$(CH_2)_m$-R_4, -O-C(O)-NH-$(CH_2)_m$-R_4, -NH-C(O)-O-$(CH_2)_m$-R_4, -O-C(S)-$(CH_2)_m$-R_4, -C(S)-O-$(CH_2)_m$-R_4, -O-C(O)-$(CH_2)_m$-R_4 or -C(O)-O-$(CH_2)_m$-R_4, or R_2, together with the R_1 that is bonded to the same carbon atom is =O;

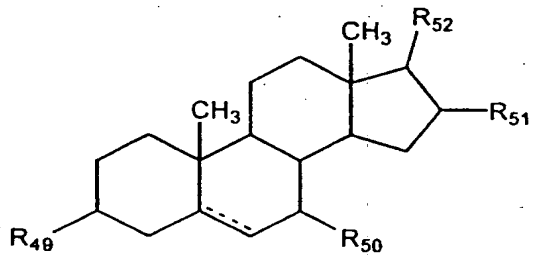
R_4 is -H, a protecting group, optionally substituted C_{1-18} alkyl, optionally substituted C_{2-18} alkenyl, optionally substituted C_{2-18} alkynyl, optionally substituted aryl, optionally substituted aryl-C_{1-6} alkyl, optionally substituted aryl-C_{2-6} alkenyl, optionally substituted aryl-C_{2-6} alkynyl, optionally substituted heterocycle-C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl-heterocycle, optionally substituted C_{2-6} alkynyl-heterocycle or an optionally substituted heterocycle, where any of the foregoing moieties are optionally substituted at one, two, three, four, five or more carbon or hydrogen atoms with one or more independently selected -O-, -S-, $-NR^{PR}$-, $-OR^{PR}$, $-NHR^{PR}$, $-SR^{PR}$, =O, =S, -CN, $-NO_2$, -F, -Cl, -Br or -I groups or atoms;

each R^{PR} independently is -H or an independently selected protecting group;

m is 0, 1, 2 or 3; and

the dotted line is an optional double bond.

15. The method of claim 1 wherein the formula 1 compound has the formula 45



45

wherein,

R_{50} is -H, -OH or =O;

R_{51} is -Br, -Cl, -F, -I or -OH;

R_{52} is -OH or, R_{52}, together with the -H bonded to the same position, is =O;

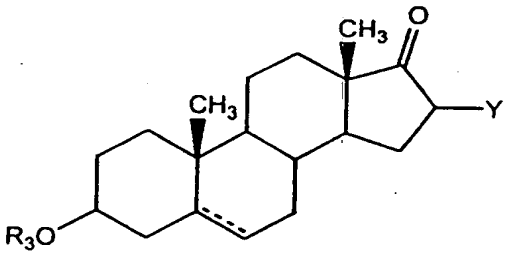
R_{49} is -H, -OH, or $-OR_{53}$;

R_{53} is C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, a C_{1-18} ester, a C_{1-18} thioester, wherein any of the foregoing C_{1-18} or C_{2-18} groups is substituted at one or more hydrogen atoms with one or more independently selected -O-, -S-, -OH, $-NH_2$, -SH or =O groups or R_{53} is a thioacetal, a sulfate ester, a sulfonate ester, a carbamate or a thioester; and

the dotted line is an optional double bond.

16. The method of claim 15 wherein R_{49} is $-O-C(O)-CH_2-CH_2-CH(R_{54})-CH(R_{55})-CH_2R_{56}$ wherein R_{54} is $-NH_2$, -OH, -SH, $-O-PO_3$, $-SO_3$ or $-OSO_3$; R_{55} is -H, $-NH_2$, -OH, -SH, $-O-PO_3$, $-SO_3$ or $-OSO_3$; and R_{56} is C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, a C_{1-18} ester or a C_{1-18} thioester, wherein any of the foregoing C_{1-18} groups is substituted at one or more hydrogen atoms with one or more independently selected -OH, $-NH_2$, -SH or =O groups.

17. The method of claim 1 wherein the formula 1 compound has the formula 44



44

wherein,

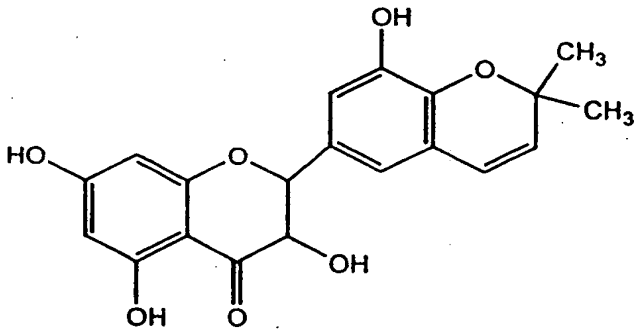
Y is hydrogen or a halogen;

R_{44} is -H, -S(O)(O)-OH, -S(O)(O)-ONa, $-S(O)(O)-O-CH_2-CH(O-C(O)-R_6)-CH_2-O-C(O)-R_6$, $-P(O)(O)-O-CH_2-CH(O-C(O)-R_7)-CH_2-O-C(O)-R_7$ or a glucuronide group of structure (A); and

the dotted line is an optional double bond.

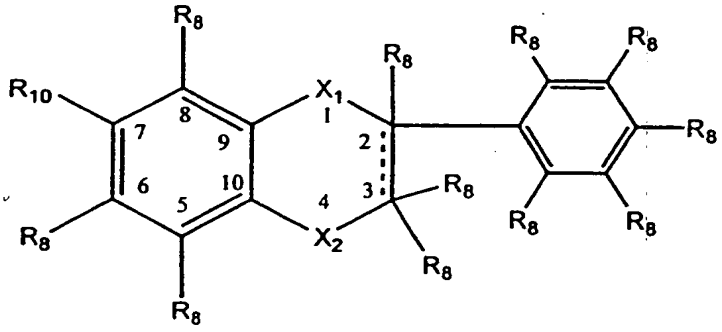
18. The method of claim 17 wherein the formula 44 compound is dehydroepiandrosterone, epiandrosterone, 16α-bromoepiandrosterone, 16α-bromodehydroepiandrosterone, dehydroepiandrosterone-3-sulfate or 5β-androstan-3β-ol-17-one.

19. The method of claim 1 wherein the method further comprises simultaneously or sequentially administering an effective amount a plasma concentration-enhancing compound selected from bavachinin A, didymin, flavanomarein, flavanone azine, flavanone diacetylhydrazone, flavanone hydrazone, silandrin, silybin, silychristin, isosilybin, a compound having the structure (E)

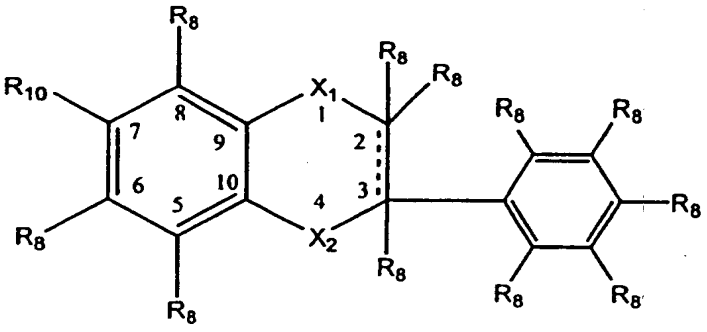


(E)

and a compound of formula 2A or 2B



2A



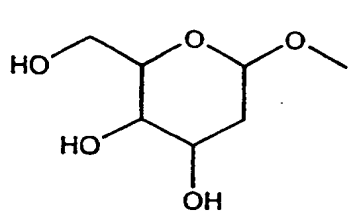
2B

wherein a double or a single bond is present at the dotted line and when a double bond is present (i) the optionally substituted phenyl ring at the 2- or 3-position is present and the R_8 that is bonded to the carbon is absent, and (ii) one R_8 at the adjacent 2- or 3-position is absent;

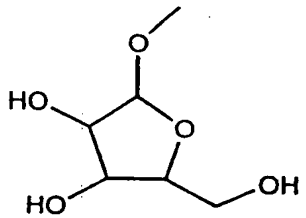
X_1 is -O- or $-C(R_8)_2-$;

X_2 is -C(O)- or $-C(R_{11})_2-$;

each R_8 independently is -H, -OH, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, glucuronide, a C_{1-25} fatty acid, the residue of a formula 2A or 2B compound where a hydrogen atom is removed to form the formula 2A or 2B compound radical, $-CH_2CH=C(CH_3)_2$, glucoside, a group having structure (B) or (C),



(B) or



(C)

R_9 is -phenyl-$(R_8)_5$, wherein one R_9 is bonded to the 2- or 3-position, but both R_9 are not bonded to both the 2- and 3-positions at the same time;

R_{10} is C_{1-6} alkyl, C_{1-6} alkoxy, neohesperidoside, apioglucoside, rutinoside, glucoside, galactoside, rhamnoside, arabinoside, or a stereoisomer, hydrate, analog, derivative or metabolite of any of these moieties, any of which are optionally independently substituted at one or more hydrogen atoms with -OH, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, glucuronide or a C_{1-25} fatty acid or R_{10} is -H, -OH or halogen;

each R_{11} independently is -H, -OH, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, a glucuronide group of structure (A), a C_{1-25} fatty acid, or both R_{11} together are =O; and

the salts, stereoisomers, positional isomers, metabolites, analogs, precursors, hydrates, tautomers, ionized forms and solvates thereof.

20. The method of claim 19 wherein the plasma concentration-enhancing compound is naringin or naringenin.

21. The method of claim 20 wherein the subject is a human or a primate.

22. The method of claim 21 wherein the formula 1 and the plasma concentration-enhancing compound are administered simultaneously.

23. The method of claim 19 further comprising administering to the subject, or treating the subject with, one or more of ribavirin, alpha interferon, a macrophage stimulating factor, an oxidation agent and oxygen ventilation.

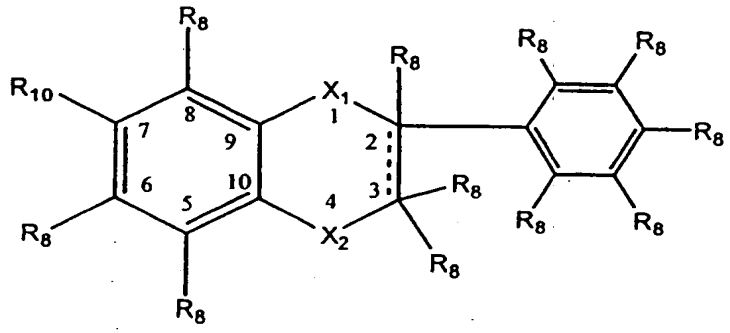
24. The method of claim 23 wherein the plasma concentration-enhancing compound is naringin or naringenin.

25. The method of claim 24 wherein the subject is a human or a primate.

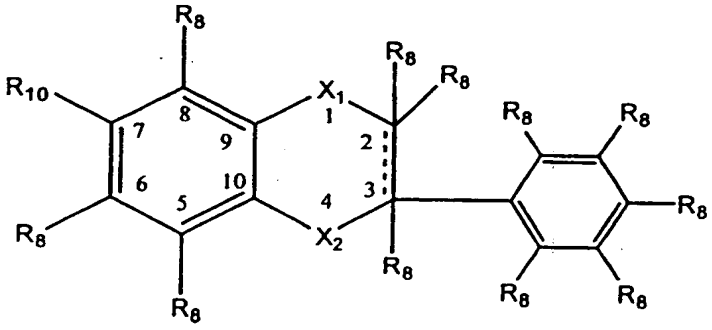
26. The method of claim 25 wherein the formula 1 compound and the plasma concentration-enhancing compound are administered simultaneously.

27. A method to enhance the oral bioavailability of a therapeutic agent comprising administering to a subject an effective amount of a compound of a plasma concentration-enhancing compound.

28. The method of claim 27 wherein the plasma concentration-enhancing compound is naringin or naringenin or the plasma concentration-enhancing compound has the formula 2A or 2B



2A



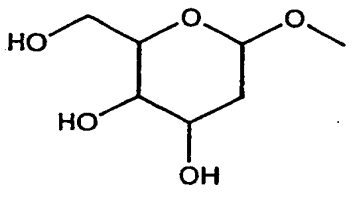
2B

wherein a double or a single bond is present at the dotted line and when a double bond is present (i) the optionally substituted phenyl ring at the 2- or 3-position is present and the R_8 that is bonded to the carbon is absent, and (ii) one R_8 at the adjacent 2- or 3-position is absent;

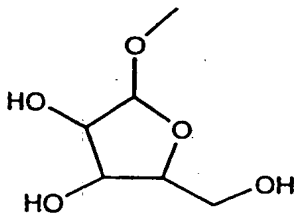
X_1 is -O- or -$C(R_8)_2$-;

X_2 is -C(O)- or -$C(R_{11})_2$-;

each R_8 independently is -H, -OH, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, glucuronide, a C_{1-25} fatty acid, the residue of a formula 2A or 2B compound where a hydrogen atom is removed to form the formula 2A or 2B compound radical, -$CH_2CH=C(CH_3)_2$, glucoside, a group having structure (B) or (C),



(B) or



(C)

R_9 is -phenyl-$(R_8)_5$, wherein one R_9 is bonded to the 2- or 3-position, but both R_9 are not bonded to both the 2- and 3-positions at the same time;

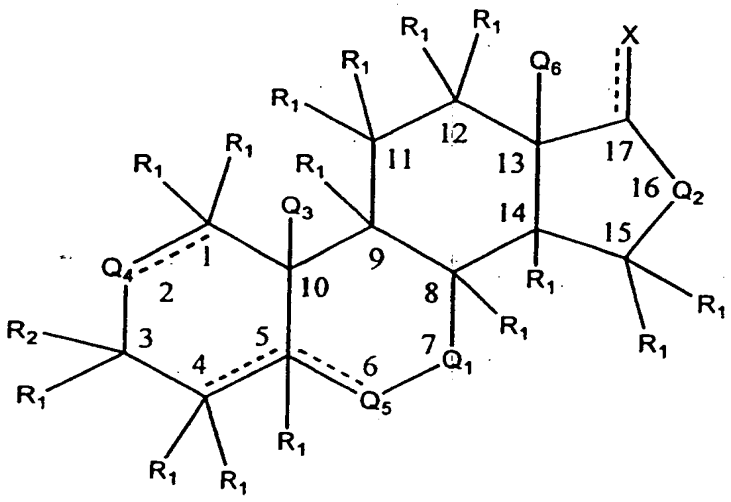
R_{10} is C_{1-6} alkyl, C_{1-6} alkoxy, neohesperidoside, apioglucoside, rutinoside, glucoside, galactoside, rhamnoside, arabinoside, or a stereoisomer, hydrate, analog, derivative or metabolite of any of these moieties, any of which are optionally independently substituted at one or more hydrogen atoms with -OH, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, glucuronide or a C_{1-25} fatty acid or R_{10} is -H, -OH or halogen;

each R_{11} independently is -H, -OH, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, a glucuronide group of structure (A), a C_{1-25} fatty acid, or both R_{11} together are =O; and

the salts, stereoisomers, positional isomers, metabolites, analogs, precursors, hydrates, tautomers, ionized forms and solvates thereof.

29. The method of claim 27 wherein the therapeutic agent is a steroid, a steroid analog an antibiotic, an antiviral agent or an antifungal agent.

30. The method of claim 27 wherein the therapeutic agent is a compound of formula 1



1

wherein

Q_1 is $-C(R_1)_2-$ or -C(O)-;

Q_2 is $-C(R_1)_2-$, $-C(R_1)(Y)-$, -C(Y)- or $-CH_2-CH_2-$;

Q_3 is -H or $-C(R_1)_3-$;

Q_4 is $-C(R_1)_2-$, -C(O)-, hydroxyvinylidine or methyl methylene;

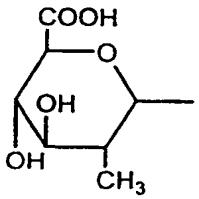
Q_5 is $-C(R_1)_2-$ or -C(O)-;

X and Y independently are -OH, -H, lower alkyl, -O-C(O)-R_5, -C(O)-OR_5, halogen or =O;

each R_1 independently is -H, halogen, -OH, C_{1-6} alkoxy, or C_{1-6} alkyl;

R_2 is -H, -OH, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, $-OR_3$, a C_{1-18} fatty acid, C_{1-10} alkynyl, $(J)_n$-phenyl-C_{1-5}-alkyl, $(J)_n$-phenyl-C_{1-5}-alkenyl, an ester, a thioester, a thioacetal, a sulfate ester, a sulfonate ester or a carbamate or R_2, together with the R_1 that is bonded to the same carbon atom is =O;

R_3 is -S(O)(O)-OM, -S(O)(O)-O-CH_2-CH(O-C(O)-R_6)-CH_2-O-C(O)-R_6, -P(O)(O)-O-CH_2-CH(O-C(O)-R_7)-CH_2-O-C(O)-R_7, a glucuronide group of structure (A)



(A)

or R_3 is C_{1-18} alkyl, C_{1-18} alkenyl, C_{1-18} alkynyl, C_{1-18} ester or C_{1-18} thioester, where any of the foregoing C_{1-18} moieties are optionally substituted at one or more hydrogen atoms with one or more independently selected -OH, $-NH_2$ or -SH groups;

each R_5 independently is straight or branched C_{1-14} alkyl;

each R_6 independently is C_{1-14} straight or branched alkyl; and

each R_7 independently is C_{1-14} straight or branched alkyl or a glucuronide group of structure (A);

n is 0, 1, 2 or 3;

each J independently is halogen, C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkoxy, carboxy, nitro, sulfate, sulfonyl, a C_{1-6} carboxyl ester or a C_{1-6} sulfate ester;

M is hydrogen, sodium, $-S(O)(O)-O-CH_2-CH(O-C(O)-R_6)-CH_2-O-C(O)-R_6$, $-P(O)(O)-O-CH_2-CH(O-C(O)-R_7)-CH_2-O-C(O)-R_7$ or a glucuronide group of structure (A); and

the dotted lines represent an optional double bond, provided that there are not double bonds at both the 4-5 and 5-6 positions and provided that when a double bond is present, zero or 1 R_1 group is bonded to carbon atoms at the 1-, 2-, 4-, 5-, 6- or 17 positions so that these carbon atoms are tetravalent; and

the salts, stereoisomers, positional isomers, metabolites, analogs, precursors, hydrates, tautomers, ionized forms and solvates thereof.

31. A method to treat or prevent a togaviral infection, or to ameliorate one or more symptoms associated with a togaviral infection, in a subject suffering from or subject to a togaviral infection, comprising administering to the subject an effective amount of a composition comprising 16α-bromoepiandrosterone, and 2, 3, 4 or 5 excipients selected from polyethylene glycol, dehydrated ethanol, benzyl benzoate, benzyl alcohol and propylene glycol, wherein the composition optionally comprises less than about 3% v/v, or less than about 1% v/v, or less than about 0.5% v/v of water, or less than about 0.1% v/v of water.

32. The method of claim 31 wherein the composition comprises 16α-bromoepiandrosterone at a concentration of about 45-55 mg/mL, 20-30% v/v polyethylene glycol 300, polyethylene glycol 400 or a mixture of polyethylene glycol 300 and 400, 10-15% v/v dehydrated ethyl alcohol, 2.5-7.5% v/v benzyl benzoate, and 55-60% v/v propylene glycol.

33. The method of claim 32 wherein the composition comprises 16α-bromoepiandrosterone at a concentration of about 50 mg/mL, about 25% v/v polyethylene glycol

300, about 12.5% v/v dehydrated ethyl alcohol, about 5% v/v benzyl benzoate, about 57.5% v/v propylene glycol and less than about 0.5% v/v water.

34. The method of claim 31 wherein the composition comprises 16α-bromoepiandrosterone at a concentration of about 85-105 mg/mL, about 27-33% w/w benzyl benzoate, about 27-33% w/w polyethylene glycol 300, about 25-30% w/w propylene glycol and about 1-3% w/w benzyl alcohol.

35. The composition of claim 34 wherein the composition comprises 16α-bromoepiandrosterone at a concentration of about 100 mg/mL, about 30.4% w/w benzyl benzoate, about 30.7% w/w polyethylene glycol 300, about 28% w/w propylene glycol and about 1.9% w/w benzyl alcohol.

36. The method of claim 1 wherein 2, 3, 4, 5 or 6 R_1 are not hydrogen.

37. The method of claim 27 wherein the 2, 3, 4, 5 or 6 R_1 that are not hydrogen are independently selected from -OH, =O, halogen and C_{2-4} alkoxy.